World Family Medicine Journal
incorporating the Middle East Journal of Family Medicine

ISSN 1839-0188

5

January-February 2026 - Volume 24 Issue 1

# Glutathione Under Scrutiny: infusion risks?

page 42

## Original Contribution and Clinical Investigation

# Editorial

**Chief Editor:**
A. Abyad
MD, MPH, AGSF, AFCHSE
Email::
aabyad@cyberia.net.lb
**Mobile:** 961-3-201901

**Publisher**
Lesley Pocock
medi+WORLD International
AUSTRALIA
**Email:**
lesleypocock@mediworld.com.au
publishermwi@gmail.com

## From Acute Events to Chronic Trajectories: Clinical Decision-Making Across the Spectrum of Modern Medicine

This issue brings together a diverse yet conceptually unified collection of clinical and scholarly contributions that reflect the evolving realities of contemporary medical practice. Although the topics range from acute respiratory emergencies to chronic metabolic disease, reproductive endocrinology, and cognitive disorders, a common thread emerges: the need for nuanced clinical judgment that integrates early recognition, individualized decision-making, and long-term outcome awareness.

The case report of persistent primary spontaneous pneumothorax in a young smoker highlights a critical lesson in frontline medicine: clinical stability can be misleading. Young patients may compensate remarkably well despite severe underlying pathology, underscoring the enduring importance of clinical suspicion, careful history taking, and timely imaging. The case also reminds clinicians that "benign-appearing" presentations may rapidly evolve into life-threatening emergencies, reinforcing the value of vigilance in primary and urgent care settings.

In contrast, the review comparing letrozole and clomiphene citrate for ovulation induction in women with polycystic ovary syndrome exemplifies how evidence-based medicine reshapes long-standing therapeutic paradigms. The shift toward letrozole as a preferred first-line agent reflects a broader movement in medicine: away from tradition-driven practice and toward outcome-oriented, patient-centered care. Beyond fertility outcomes, this discussion highlights the importance of minimizing treatment-related harm while optimizing long-term reproductive and metabolic health.

The concept paper proposing obesity as an irreversible atherosclerotic endpoint challenges conventional thinking by reframing obesity not merely as a risk factor, but as a structural and systemic manifestation of chronic endothelial injury. This perspective compels clinicians to reconsider prevention timelines, therapeutic targets, and the biological limits of reversibility. It also aligns with growing recognition that cardiometabolic diseases, once established, often represent cumulative vascular damage rather than isolated metabolic disturbances.

Finally, the comprehensive review on vascular dementia illustrates how advances in neuroimaging, neuropathology, and cognitive neuroscience have transformed our understanding of late-life cognitive impairment. The increasing recognition of mixed dementia—where vascular injury interacts with neurodegenerative pathology—reinforces the importance of aggressive vascular risk factor control across the lifespan. Cognitive decline, in this context, becomes not an inevitable consequence of aging, but a partially preventable outcome shaped by decades of vascular health.

Taken together, the contributions in this issue reflect medicine's shifting focus from episodic disease management toward longitudinal, systems-based thinking. Acute events are no longer viewed in isolation, and chronic conditions are increasingly understood as the downstream consequences of earlier biological and behavioral trajectories. This integrated perspective is particularly relevant for clinicians practicing in primary care, internal medicine, geriatrics, and family medicine, where continuity of care and early intervention are paramount. We hope this issue encourages readers to look beyond diagnostic labels and immediate outcomes, and instead to consider how early recognition, evidence-guided choices, and preventive strategies can meaningfully alter disease trajectories. In doing so, it reaffirms a central principle of modern medicine: that thoughtful clinical judgment remains as essential as ever, even in an era of expanding technology and specialization.

In closing, this issue deliberately foregrounds two papers that challenge prevailing clinical narratives and invite readers to reconsider how widely accepted concepts are defined, communicated, and applied in practice. The conceptual paper redefining obesity through the lens of excess fat tissue rather than body weight alone directly confronts the limitations of traditional BMI-based classifications, reframing adiposity as a cumulative, systemic, and often irreversible manifestation of chronic endothelial injury. This perspective has profound implications for prevention, clinical counseling, and the realistic expectations of reversibility in cardiometabolic disease. In parallel, the critical review of glutathione for skin lightening exemplifies the editorial responsibility to scrutinize emerging, and often commercially driven therapies, clearly distinguishing between cautiously supported oral and topical use and the ethically and clinically concerning practice of unregulated intravenous administration. Together, these papers reinforce a central editorial message of this issue: modern clinical practice must move beyond surface-level metrics and short-term outcomes, and instead be anchored in pathophysiology, long-term risk assessment, regulatory responsibility, and patient safety. By challenging complacency in both metabolic medicine and aesthetic therapeutics, these contributions exemplify the role of scholarly journals not merely as repositories of information, but as active forums for critical reflection, professional accountability, and evidence-informed clinical judgment.

Warm regards,
**Dr. Abdulrazak Abyad**
**Editor-in-Chief**
**MEJFM**

# Obesity may be an irreversible atherosclerotic endpoint in the human body

Mehmet Rami Helvaci[1], Esma Helvaci[1], Emine Helvaci[2], Yusuf Aydin[1], Leyla Yilmaz Aydin[3], Alper Sevinc[1], Celaletdin Camci[1]

1- Specialist of Internal Medicine, MD, Turkey
2- Manager of Writing and Statistics, Turkey
3- Specialist of Pulmonary Medicine, MD, Turkey

**Correspondence**
Prof Dr Mehmet Rami Helvaci
07400, ALANYA, Turkey
Phone: 00-90-506-4708759
**Email:** mramihelvaci@hotmail.com

Received: November 2025. Accepted: December 2025; Published: January/February 2026.
Citation: Helvaci MR et al. Obesity may be an irreversible atherosclerotic endpoint in human body. World Family Medicine. January/February 2026; 24(1): 5 - 21. DOI: 10.5742/MEWFM.2026.2401021

## Abstract

Methods: Sickle cell diseases (SCD) patients were studied.

Results: We studied 222 males and 212 females (30.8 vs 30.3 years of age, 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), stroke (12.1% vs 7.5%, p<0.05), chronic renal disease (CRD) (9.9% vs 6.1%, p<0.05), cirrhosis (8.1% vs 1.8%, p<0.001), chronic obstructive pulmonary disease (25.2% vs 7.0%, p<0.001), coronary heart disease (18.0% vs 13.2%, p<0.05), leg ulcers (19.8% vs 7.0%, p<0.001), and digital clubbing (14.8% vs 6.6%, p<0.001) were all higher in males, significantly.

Conclusion: As an accelerated atherosclerotic process, hardened RBC-induced capillary endothelial damage terminates with end-organ insufficiencies in early decades of life in SCD. Although atherosclerotic endpoints are so common, we detected no case of diabetes mellitus (DM) probably due to lower excess fat tissue. As the most common cause of CRD, DM may be a relative insufficiency of pancreas against the excess fat tissue. Increased blood and insulin requirements of excess fat in contrast to decreased blood supply of excess tissue and pancreas both due to excess external pressure and internal narrowing of vasculature may be important for DM. As the most common cause of DM, obesity may be an irreversible atherosclerotic endpoint in human body. Acarbose and metformin are oral, safe, cheap, and effective drugs to prevent obesity.

Key words: Sickle cell diseases, excess fat tissue, obesity, acarbose, metformin, endothelial inflammation, atherosclerosis

## Introduction

Chronic endothelial damage initiated at birth may be the most common cause of aging and death via the atherosclerotic endpoints in human being (1). Much higher blood pressures (BP) of the arterial system may be the strongest accelerating factor by means of the repeated injuries on vascular endothelium. Probably, whole afferent vasculature including capillaries are chiefly involved in the catastrophic process. Therefore venosclerosis is not a significant health problem in medicine. Due to the chronic endothelial damage, inflammation, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic natures, which terminally reduce blood supply to the end-organs, and increase systolic and decrease diastolic BP further. Some of the well-known accelerating factors of the inflammatory process are physical inactivity, emotional stress, animal-rich diet, smoking, alcohol, excess fat tissue, chronic inflammation, prolonged infection, and cancers for the development of atherosclerotic endpoints including obesity, hypertension (HT), diabetes mellitus (DM), chronic renal disease (CRD), coronary heart disease (CHD), cirrhosis, chronic obstructive pulmonary disease (COPD), peripheric artery disease (PAD), stroke, abdominal angina, osteoporosis, dementia, aging, and death (2, 3). Although early withdrawal of the accelerating factors can delay the atherosclerotic endpoints, the endothelial changes can not be reversed, completely due to fibrotic natures. The accelerating factor and atherosclerotic endpoints have been researched under the titles of metabolic syndrome, aging syndrome, and accelerated endothelial damage syndrome in the literature, extensively (4-6). Similarly, sickle cell diseases (SCD) are highly catastrophic process on vascular endothelium initiating at birth and terminating with an accelerated atherosclerosis-induced end-organ insufficiencies even at childhood (7, 8). Hemoglobin S causes loss of elastic and biconcave disc shaped structures of red blood cells (RBC). Loss of elasticity instead of shape may be the main problem because the sickling is rare in peripheric blood samples of cases with associated thalassemia minors (TM), and survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during whole lifespan, but exaggerated with inflammation, infection, cancer, surgery, and emotional stress. The hardened RBC-induced chronic endothelial damage, inflammation, and fibrosis terminate with tissue hypoxia in whole body (9). As a difference from other causes of chronic endothelial damage, SCD keep vascular endothelium particularly at the capillary level since the capillary system is the main distributor of the hardened RBC into the body (10, 11). The hardened RBC-induced chronic endothelial damage builds up an accelerated atherosclerosis in earlier decades of life. Vascular narrowing and obstructions-induced tissue ischemia and end-organ insufficiencies are the terminal consequences, so the mean life expectancy is decreased 30 years or more in the SCD because we have patients with the age of 96 years without the SCD but just with the age of 59 years with the SCD (8).

## Materials and Methods

The study was performed in the Medical Faculty of the Mustafa Kemal University between March 2007 and June 2016. All cases with the SCD were included. SCD are diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Smoking, alcohol, acute painful crises per year, transfused units of RBC in their lifespans, leg ulcers, stroke, surgeries, deep venous thrombosis (DVT), epilepsy, and priapism were researched in all patients. Cases with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers. A physical examination was performed by the Same Internist, and patients with disseminated teeth losses (<20 teeth present) were detected. Patients with acute painful crisis or any other inflammatory or infectious process 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 magnetic resonance imagings (MRI) of brain and hips were performed. Other bones for avascular necrosis were scanned according to the patients' complaints. Avascular necrosis of bones is diagnosed via MRI (12). Associated TM were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC since SCD with associated TM come with milder clinics than the sickle cell anemia (SCA) (Hb SS) alone (13). Systolic BP of the pulmonary artery of 40 mmHg or greater are accepted as pulmonary hypertension (14). Cirrhosis is diagnosed with full physical examination, laboratory parameters, and ultrasonographic evaluation of the liver. 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, dyspnea, and 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 is diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity. CRD is diagnosed with a permanently elevated serum creatinine level of 1.3 mg/dL or higher in males and 1.2 mg/dL or higher in females. 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 taken in case of an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is performed in case of

a positive exercise electrocardiogram. As a result, CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as movement disorders in the heart walls. Rheumatic heart disease is diagnosed with the echocardiographic findings, too. Stroke is diagnosed by the CT and/or MRI of the brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in case of visual complaints. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

## Results

We included 222 males and 212 females with similar mean ages (30.8 vs 30.3 years, p>0.05, respectively) into the study, and there was no patient above the age of 59 years. Associated TM were detected with similar prevalences in both genders (72.5% vs 67.9%, p>0.05, respectively). Smoking (23.8% vs 6.1%) and alcohol (4.9% vs 0.4%) were both 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), CRD (9.9% vs 6.1%, p<0.05), cirrhosis (8.1% vs 1.8%, p<0.001), COPD (25.2% vs 7.0%, p<0.001), CHD (18.0% vs 13.2%, p<0.05), 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. 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, the mean ages of the atherosclerotic endpoints 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)* |
| *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)* |
| *CRD*** | *9.9% (22)* | *<0.05* | *6.1% (13)* |
| *Stroke* | *12.1% (27)* | *<0.05* | *7.5% (16)* |
| PHT*** | 12.6% (28) | Ns | 11.7% (25) |
| Autosplenectomy | 50.4% (112) | Ns | 53.3% (113) |
| DVT**** and/or varices and/or telangiectasias | 9.0% (20) | Ns | 6.6% (14) |
| Rheumatic heart disease | 6.7% (15) | Ns | 5.6% (12) |
| Avascular necrosis of bones | 24.3% (54) | Ns | 25.4% (54) |
| Sickle cell retinopathy | 0.9% (2) | Ns | 0.9% (2) |
| Epilepsy | 2.7% (6) | Ns | 2.3% (5) |
| 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 §Coronary heart disease
¶ Chronic obstructive pulmonary disease **Chronic renal disease ***Pulmonary hypertension
****Deep venous thrombosis *****Acute chest syndrome

**Table 3: Mean ages of endpoints 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 vasculitis and aging, and obesity may be an irreversible atherosclerotic endpoint in human body. Excess fat tissue causes both excess external pressure and internal narrowing of vasculature in addition to the already increased blood and insulin needs of the excess tissue. DM may be an irreversible atherosclerotic consequence caused by the excess fat tissue in whole body rather than the pancreas alone. Although all kinds of atherosclerotic consequences are so common with the SCD, we have detected no case of DM, probably due to the lower excess fat tissue in them (10). The body mass indexes (BMI) were 20.7 vs 24.9 kg/m2 in the SCD and control groups, respectively with the mean age of 28.6 years (p= 0.000) (10). The body heights were similar in both groups (166.1 vs 168.5 cm, respectively, p>0.05) which may indicate that the height is determined, genetically (10). Similarly, just 20% of elderly have DM, but 55% of patients with DM are obese. So excess fat tissue may be more risky than aging, smoking, alcohol, or chronic inflammatory or infectious processes for the development of DM. Excess fat tissue leads to a chronic and low-grade inflammation on vascular endothelium, and risk of death from all causes increases parallel to its severity (19). The low-grade chronic inflammation may also cause genetic changes on the endothelial cells, and the systemic atherosclerotic process may even decrease clearance of malignant cells by the natural killers (20). The chronic inflammatory process is characterized by lipid-induced injury, invasion of macrophages, proliferation of smooth muscle cells, endothelial dysfunction, and increased atherogenicity (21, 22). Excess fat tissue is considered as a strong factor for controlling of C-reactive protein (CRP) since the excess tissue produces biologically active leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines (23, 24). On the other hand, excess fat tissue will also aggravate myocardial hypertrophy and decrease cardiac compliance. Fasting plasma glucose (FPG), triglycerides, and low density lipoproteins (LDL) increased and high density lipoproteins (HDL) decreased parallel to the severity of BMI (25). Similarly, CHD and stroke increased parallel to the severity of BMI (26). Eventually, the risk of death from all causes increased parallel to the severity of excess fat tissue in all age groups, and people with underweight may even have lower biological ages and longer overall survival (27). Similarly, calorie restriction prolongs survival and retards age-related chronic sicknesses (28). So the term of excess weight should be replaced with the amount of excess fat tissue in human body since there are nearly 19 kg of excess fat tissue even between the lower and upper borders of normal weight in adults.

Smoking may be the second most common cause of vasculitis all over the body. It causes a systemic inflammation on vascular endothelium terminating with atherosclerotic endpoints (29). Its atherosclerotic effects are the most obvious in the Buerger's disease and COPD (30). Buerger's disease is an obliterative vasculitis in the small and medium-sized arteries and veins, and it has never been reported in the absence of smoking in the literature. Its characteristic features are chemical toxicity, inflammation, fibrosis, and narrowing and occlusions of arteries and veins. Claudication is the most significant symptom with a severe pain in feet and hands caused by insufficient blood supply during exercise. It may also radiate to central areas in advanced cases. Numbness or tingling of the limbs is also a common symptom in them. Skin ulcerations and gangrene of fingers or toes are the terminal endpoints. 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 the main cause of severity of Buerger's disease in the lower extremities. Several narrowing and occlusions of the arm and legs are diagnostic in the angiogram. Skin biopsies may be risky, because a poorly perfused area will not heal, completely. Although most patients are heavy smokers, the limited smoking history of some patients may support the hypothesis that Buerger's disease may be an autoimmune reaction triggered by some constituents of tobacco. Although the only treatment way is complete cessation of smoking, the already developed narrowing and occlusions are irreversible. Due to the well-known role of inflammation, anti-inflammatory dose of aspirin in addition to the low-dose warfarin may even be life threatening by preventing microvascular infarctions. On the other hand, FPG and HDL may be negative whereas triglycerides, LDL, erythrocyte sedimentation rate, and CRP positive acute phase reactants (APR) in smokers (31). Similarly, smoking was associated with the lower BMI due to the systemic inflammatory effects (32, 33). An increased heart rate was detected just after smoking even at rest (34). Nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner (35). 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 white coat hypertension, BMI, LDL, triglycerides, HT, and DM in females (38). The risk of myocardial infarction is increased three-fold in men and six-fold in women with smoking (39). Chemical toxicity of smoking can affect all organ systems. For instance, it is usually associated with irritable bowel syndrome (IBS), chronic gastritis, hemorrhoids, urolithiasis, and depression with many possible mechanisms (40). First of all, smoking may also have some anxiolytic properties. Secondly, smoking-induced vascular inflammation may disturb epithelial absorption and excretion in the gastrointestinal (GI) and genitourinary (GU) tracts (41). Thirdly, diarrheal losses-induced urinary changes may cause urolithiasis (42). Fourthly, smoking-induced sympathetic nervous system activation may cause motility problems in the GI

and GU tracts terminating with IBS and urolithiasis. Finally, immunosuppression secondary to smoking may terminate with the GI and GU tract infections and urolithiasis because some types of bacteria can provoke urinary supersaturation, and modify the environment to form crystal deposits. Actually, 10% of urinary stones are struvite stones which are built by magnesium ammonium phosphate produced by the urease producing bacteria. As a result, urolithiasis was higher in the IBS patients, significantly (17.9% vs 11.6%, p<0.01) (40).

CHD is the other major cause of death in the human being together with the stroke. The most common triggering cause is the disruption of an atherosclerotic plaque in an epicardial coronary artery, which leads to a clotting cascade. The plaques are the gradual and unstable collection of lipids, fibrous tissue, and white blood cells (WBC), particularly the macrophages in arterial walls in decades of life. 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 takes its place which may also cause life threatening arrhythmias because the scar tissue conducts electrical impulses more slowly. The difference in conduction velocity between the injured and uninjured tissues can trigger re-entry or a feedback loop that is believed to be the cause of 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. Ventricular tachycardia may also cause sudden cardiac death that usually results in rapid heart rates preventing effective cardiac pumping. Cardiac output and BP may fall to dangerous levels which can lead to further coronary ischemia and extension of the infarct. This scar tissue may even cause ventricular aneurysm and rupture. Aging, physical inactivity, animal-rich diet, excess fat tissue, smoking, alcohol, emotional stress, prolonged infection, chronic inflammation, and cancers are important in atherosclerotic plaque formation. Moderate physical exercise is associated with a 50% reduced incidence of CHD (43). Probably, excess fat tissue may be the most important cause of CHD because there are approximately 33 kg of excess fat tissue between the lower borders of normal weight and obesity, and 66 kg between the lower borders of normal weight and morbid obesity (BMI ≥ 40 kg/m2) in adults. In other definition, there is a high percentage of adults with heavier fat tissue masses than their lean body masses that brings a greater stress on the heart, liver, kidneys, lungs, brain, and pancreas.

DM is the most common cause of blindness, non-traumatic amputation, and hemodialysis in adults. As the most common cause of CRD, DM may be an irreversible atherosclerotic consequence affecting the pancreas, too. Increased blood and insulin needs of the excess fat tissue in contrast to the decreased blood supply of the excess tissue and pancreas both due to excess external pressure and internal narrowing of the vasculature may be the underlying mechanisms of DM. For instance, excess fat tissue in the liver and pancreas are called as non-alcoholic fatty liver disease (NAFLD) and non-alcoholic fatty pancreas disease (NAFPD). They are usually accepted as components of the metabolic syndrome. NAFLD progresses to steatohepatitis, cirrhosis, and hepatocellular carcinoma. Blocking triglycerides secretion, subcellular lipid sequestration, lipolysis deficiency, enhanced lipogenesis, gluconeogenesis defects, or inhibition of fatty acid oxidation may be some of the development mechanisms (44). NAFLD may just be an atherosclerotic process, and strongly associated with an accelerated atherosclerotic process not only in the liver instead in whole body. For example, NAFLD is seen in one-third of cases with hepatitis B virus-related chronic liver disease (45). Similarly, higher fatty liver ratios were observed in children with non-Hodgkin lymphomas (46). The liver density on contrast abdominopelvic CT of colorectal cancer patients was low that is consistent with the NAFLD (47). As one of the APR, serum thrombopoietin levels increased in the NAFLD (48). Although serum levels of oxidizing agents including nitrate and advanced oxidation protein products increased, serum nitrite did not adequately increase as an antioxidant agent in the NAFLD (49). As a result, NAFLD is associated with an impaired carotid intima-media thickness (IMT) and flow-mediated dilation which are considered as early markers of systemic atherosclerosis (50). Carotid IMT was correlated with the BMI (p<0.001), age (p= 0.001), and grade 2-3 NAFLD (p<0.001) (51). Patients with the NAFLD have more complex CHD, and carotid IMT and grade 2-3 NAFLD were associated with the severity of CHD (p<0.001 for both) (51-53). Similarly, there were reductions in hepatic artery flow volume, portal vein flow volume, and total flow volume in contrast to the increased NAFLD (54). As the most common pathology of pancreas in adults, there may be reductions in flow volume of pancreatic arteries in the NAFPD, too (55). NAFPD is usually associated with the aging, increased BMI, and insulin resistance (56). Replacement of more than 25% of pancreas by fat tissue is associated with the risks of systemic atherosclerosis and DM (57). Insulin is stored in vacuoles in beta cells of islets of Langerhans in whole pancreas and released via exocytosis. Pancreatic fat infiltration may lead to a reduced insulin secretion (58). NAFPD may lead to exocrine pancreatic insufficiency by fat droplet accumulation in pancreatic acinar cells and consequent lipotoxicity, destruction of acinar cells by both inflammation and fatty replacement, and by negative paracrine effect of adipocytes (59). It is unsurprising that the NAFPD may even cause pancreatic fibrosis and cancers. NAFPD causes a higher risk of DM (57), and newly diagnosed patients with DM have higher pancreatic fat (60). DM may actually be a relative insufficiency of the pancreas against the excess fat tissue in whole body. Age-related impairment of beta cells may actually be an atherosclerotic endpoint since 20% of elderly have DM, and just 55% of patients with DM are obese. Glucose tolerance progressively decreases by aging. It may be due to the progressively decreased physical and mental activity-induced excess fat tissue secreting adipokines. There is no term of malnutrition-related DM. DM can be cured by gastric bypass surgery in 90% of morbid obese

cases (61). The effect is not due to the weight loss instead decreased insulin requirement daily because it usually occurs just after days of the surgery. This surgery reduced death rate from all causes by 40% (61). NAFPD is an independent risk factor for CHD, too (62). Similarly, NAFPD is associated with increased aortic IMT and epicardial fat tissue (63). As a result, NAFLD, cirrhosis, NAFPD, and DM may be some irreversible atherosclerotic endpoints in human body (64).

Acute painful crises are nearly pathognomonic for the SCD. Although some authors reported that pain itself may not be life threatening directly, infection, medical or surgical emergency, or emotional stresses are the most common precipitating factors of the crises (65). The increased basal metabolic rate during such stresses aggravates the sickling and capillary endothelial damage, inflammation, and edema terminating with tissue hypoxia and end-organ insufficiencies in whole body. So the risk of mortality is much higher during such crises. Actually, each crisis may complicate with the following crises by leaving sequelaes on the capillary endothelial system all over the body. After a period of time, the sequelaes may terminate with end-organ failures and sudden death with a silent painful crisis, 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 (66, 67). Rapid RBC supports are usually life-saving, although preparation of RBC units usually takes a period of time. Beside that RBC supports in emergencies become much more difficult in terminal cases due to the repeated transfusions and interestingly aging-induced blood group mismatch. Actually, transfusion of each unit complicates the following transfusions via the blood subgroup mismacth. Due to the efficacy of hydroxyurea, RBC transfusions should be preserved just for acute stress and emergencies (66-68). According to our experiences, simple and repeated transfusions are superior to exchange (69, 70). First of all, preparation of one or two units of RBC suspensions in each time provides time to clinicians by preventing sudden death. Secondly, transfusions of one or two units in each time decrease the severity of pain, and relax the patients and their relatives since RBC transfusions probably have the strongest analgesic effects (71). Actually, the decreased severity of pain by transfusions also indicates the decreased severity of inflammation in whole body. Thirdly, transfusions of lesser units will decrease transfusion-related complications including infections, iron overload, and blood group mismatch. Fourthly, transfusions in the secondary health centers prevent deaths developed during the transport to the tertiary centers for the exchange. Terminally, cost of the simple transfusions on insurance system is much lower than the exchange which 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. Probably, leukocytosis contributes to the pathogenesis by releasing cytotoxic enzymes. The adverse effects of WBC on vascular endothelium are of particular interest for atherosclerotic endpoints. For example, leukocytosis even in the absence of any infection was an independent predictor of the severity of the SCD (72), and it was associated with the risk of stroke (73). Disseminated tissue hypoxia, releasing of inflammatory mediators, bone infarctions, and activation of afferent nerves may take role in the pathophysiology of the intolerable pain. Due to the severity of pain, narcotic analgesics are usually required (74), but simple transfusions are effective both to relieve pain and to prevent sudden deaths which may develop due to the end-organ failures on atherosclerotic background of the SCD.

Hydroxyurea is the life-saving drug for the SCD. It interferes with the cell division by blocking the formation of deoxyribonucleotides via the 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 (75, 76). 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 catastrophic process is probably exaggerated by the patients' own WBC and PLT. So suppression of proliferation of them can limit the endothelial damage-induced edema, ischemia, and infarctions (77). Similarly, Hb F levels in hydroxyurea users did not differ from their pretreatment levels (78). 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 (79). The study particularly researched effects of hydroxyurea on painful crises, ACS, and need of RBC transfusion. The outcomes were so overwhelming in the favour of hydroxyurea group 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 (79). In multivariable analyses, there was a strong and independent association of lower neutrophil counts with the lower crisis rates (79). 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, annually (79). 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, annually ($p<0.000$) with an additional decreased severity of them (7.8/10 vs 2.2/10, $p<0.000$) (66). Similarly, adults using hydroxyurea for frequent painful crises appear to have reduced mortality rate after a 9-year follow-up period (80). Although the genetic severity remains as the main factor to determine prognosis, hydroxyurea may decrease severity of disease and prolong survival (80). The complications start to be seen even after birth. For example, infants with lower hemoglobin levels were more likely to have higher incidences of ACS, painful crises, and

lower neuropsychological scores, and hydroxyurea reduced the incidences of all (81). If started early, hydroxyurea may protect splenic function, improve growth, and delay atherosclerotic endpoints. But due to the risks of infections, iron overload, and development of allo-antibodies causing subsequent transfusions much more difficult, RBC transfusions should be preserved for acute stress and emergencies as the most effective weapon in our hands.

Aspirin is a member of nonsteroidal anti-inflammatory drugs (NSAID). Although aspirin has similar anti-inflammatory effects with the other NSAID, it also suppresses the normal functions of PLT, irreversibly. 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 the synthesis of prostaglandins (PG) and thromboxanes (TX). 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. TX are responsible for the aggregation of PLT to form blood clots. Low-dose aspirin 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 anymore. But aspirin has no effect on the blood viscosity. The antithrombotic property is useful to reduce the risks of myocardial infarction, transient ischemic attack, and stroke (82). Low-dose of aspirin is effective to prevent the second myocardial infarction, too (83). Aspirin may also be effective in prevention of colorectal cancers (84). 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 should not be prescribed for febrile patients under the age of 12 years (85), and it was only recommended for Kawasaki disease (86). Reye syndrome is a rapidly worsening brain disease (86). The first detailed description of Reye syndrome was in 1963 by an Australian pathologist, Douglas Reye (87). The syndrome mostly affects children, but it can only affect fewer than one in a million children, annually (87). Symptoms of Reye syndrome may include personality changes, confusion, seizures, and loss of consciousness (86). Although the liver toxicity and enlargement typically occurs in most cases, jaundice is usually not seen (86). Although the death occurs in 20-40% of affected cases, about one third of survivors get a significant degree of brain damage (86). It usually starts just after recovery from a viral infection, such as influenza or chicken pox. About 90% of children are associated with an aspirin use (87, 88). 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 (86). When aspirin was withdrawn for children in the US and UK, a decrease of more than 90% in rates of Reye syndrome was seen in the 1980s (87). Due to the much lower risk of Reye syndrome but much higher risk of death, aspirin must be added into the acute and chronic phase treatments with an anti-inflammatory dose even in childhood in the SCD (89).

Warfarin is an anticoagulant, and it has no effect on blood viscosity, too. It is the best suited for anticoagulation in areas of slowly flowing blood such as veins and the pooled blood behind artificial and natural valves and dysfunctional cardiac atria. It is commonly used to prevent DVT and pulmonary embolism, and against stroke in atrial fibrillation (AF), valvular heart disease, and artificial heart valves. It is additionally used following ST-segment elevation myocardial infarction and orthopedic surgeries. Initiation regimens are simple, safe, and suitable to be used in the ambulatory settings (90). It should be initiated with a 5 mg dose, or 2 to 4 mg in the elderlies. In the protocol of low-dose warfarin, the target international normalised ratio (INR) is between 2.0 and 2.5, whereas in the protocol of standard-dose warfarin, the target INR is between 2.5 and 3.5 (91). Simple discontinuation of the drug for five days is enough to reverse the effect, and causes INR to drop below 1.5 (92). Its effects can be reversed with phytomenadione (vitamin K1), fresh frozen plasma, or prothrombin complex concentrate, rapidly. Warfarin decreases blood clotting by blocking vitamin K epoxide reductase, an ezyme that reactivates vitamin K1. Without sufficient active vitamin K1, abilities of clotting factors II, VII, IX, and X are decreased. The abilities of anticlotting protein C and S are also inhibited, but to a lesser degree. A few days are required for full effect which is lasting up to five days. The consensus agrees that current self-testing and management devices are effective providing outcomes possibly better than achieved, clinically. The risk of severe bleeding is just 1-3%, annually, and the severest ones are those involving the central nervous system (92, 93). The risk is particularly increased once the INR exceeds 4.5 (93). The risk of bleeding is increased further when warfarin is combined with antiplatelet drugs such as clopidogrel or aspirin (94). Thirteen publications from 11 cohorts including more than 48.500 patients with more than 11.600 warfarin users were included in the meta-analysis in which warfarin resulted with a lower risk of ischemic stroke ($p= 0.004$) and mortality ($p<0.00001$), but had no effect on major bleeding ($p>0.05$) in patients with AF and non-end-stage CRD (95). Warfarin is associated with significant reductions in ischemic stroke even in patients with warfarin-associated intracranial hemorrhage (ICH) (96). On the other hand, patients with cerebral venous thrombosis (CVT) anticoagulated either with warfarin or dabigatran had lower risk of recurrent venous thrombotic events (VTE), and the risks of bleeding were similar in both regimens (97). Additionally, an INR value of 1.5 achieved with an average daily dose of 4.6 mg warfarin, has resulted with no increase in the number of men ever reporting minor bleeding episodes (98). Non-rheumatic AF increases the risk of stroke, and long-term use of low-dose warfarin is highly effective and safe with a

reduction of 86% (p= 0.0022) (99). The mortality rate was significantly lower in the warfarin group, too (p= 0.005) (99). The frequencies of bleedings that required hospitalization or transfusions were similar in both groups (p>0.05) (99). Additionally, very-low-dose warfarin was safe and effective for prevention of thromboembolism in metastatic breast cancer in which the average daily dose was 2.6 mg, and the mean INR value was 1.5 (100). 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 bleedings as for warfarin, but increased GI bleeding (101). Interestingly, rivaroxaban and low-dose apixaban were associated with increased risks of all cause mortality compared with warfarin (102). The mortality rates were 4.1%, 3.7%, and 3.6% per year in the warfarin, 110 mg of dabigatran, and 150 mg of dabigatran groups with AF, respectively (p>0.05 for both) (103). Eventually, infection, inflammation, medical or surgical emergency, and emotional stress-induced increased basal metabolic rate accelerates sickling, and an exaggerated capillary endothelial edema-induced myocardial infarction or stroke may cause sudden deaths (104). So anti-inflammatory dose of aspirin plus low-dose warfarin may be the other life-saving drug regimen to prevent atherosclerotic endpoints even at childhood in the SCD (105).

COPD is the third leading cause of death at the moment (106). Aging, smoking, alcohol, male gender, excess fat tissue, chronic inflammation, prolonged infection, and cancers may be the 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 second common cause of COPD due to the excess fat tissue-induced atherosclerotic endpoints in whole body since an estimated 25-45% of patients with the COPD have never smoked (107). Regular alcohol consumption may be the third leading cause of the systemic exaggerated 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 endothelial cells is exaggerated by release of various chemicals by inflammatory cells, and it terminates with an advanced fibrosis, atherosclerosis, and pulmonary losses. COPD may just be the pulmonary endpoint of the systemic atherosclerotic process since there are several reports about coexistence of associated endothelial inflammation in whole body in the 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 multicenter study of 5.887 smokers (112). When 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). Finally, COPD may also be an irreversible atherosclerotic endpoint in the SCD (106).

Leg ulcers are seen in 10% to 20% of patients with the SCD, and its prevalence increases with aging, male gender, and SCA (114, 115). The leg ulcers have an intractable nature, and around 97% of them relapse in 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 main 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. Smoking and alcohol probably have some additional atherosclerotic effects on the leg ulcers in males. Although presence of a continuous damage of hardened RBC on vascular endothelial cells, severity of the destructive process is probably exaggerated by the immune system. The main action way of hydroxyurea may be the suppression of hyperproliferative WBC and PLT in the SCD (117). Similarly, lower WBC counts were associated with lower crisis rates, and if a tissue infarct occurs, lower WBC counts may decrease severity of tissue damage and pain (78). 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 cell edema.

Digital clubbing is characterized by the increased normal angle of 165° between the nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (118). The chronic tissue hypoxia is highly suspected in its etiology (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 smoking and pulmonary, cardiac, renal, and hepatic diseases which are characterized with chronic tissue hypoxia (5). As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs those can affect their functions in a short period of time. On the other hand, digital clubbing is also common in the SCD, too and its prevalence is 10.8% in the present study. It probably shows chronic tissue hypoxia caused by disseminated endothelial damage, edema, and fibrosis, particularly at the capillary level in the SCD. Beside the effects of SCD, smoking, alcohol, cirrhosis, CRD, CHD, and COPD, the higher prevalence of clubbing in males (14.8% vs 6.6%,

p<0.001) may also indicate some additional role of male gender for the atherosclerotic endpoints.

CRD is increasing which can be explained by prolonged survival and increased prevalence of excess fat tissue, too (120). Aging, animal-rich diet, excess fat tissue, smoking, alcohol, chronic inflammatory or infectious process, and cancers may be the major causes of the renal endothelial inflammation, too. The 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 (121). Excess fat tissue-induced hyperglycemia, dyslipidemia, elevated BP, and insulin resistance can cause tissue inflammation and immune cell activation (122). Age (p= 0.04), high-sensitivity CRP (p= 0.01), mean arterial BP (p= 0.003), and DM (p= 0.02) had significant correlations with the CIMT (120). 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 (123). 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 (123). However, along with the increased BP, these changes cause a hemodynamic burden on the kidneys in long term that causes chronic endothelial damage (124). 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, CRD progresses more easily (123). The systemic inflammatory effects of smoking on endothelial cells is also important in the CRD (125). Although the presence of some opposite reports (125), alcohol probably gives harm to the renal vascular endothelium, too. Chronic inflammatory or infectious processes may also terminate with atherosclerotic endpoints in kidneys (124). There are close relationships between CRD and other atherosclerotic endpoints (126, 127). The most common causes of death were CHD and stroke in CRD, again (128). The hardened RBC-induced capillary endothelial damage may be the major cause of CRD in the SCD, again (129).

Stroke is the other terminal cause of death, together with the CHD, and it develops as an acute thromboembolic event on the chronic atherosclerotic background. Aging, male gender, smoking, alcohol, excess fat tissue, chronic inflammatory or infectious process, cancer, and emotional stress may be the major causes. Stroke is also a common atherosclerotic endpoint of the SCD (130). Similar to the leg ulcers, stroke is particularly higher in cases with the SCA and higher WBC counts (131). Sickling-induced capillary endothelial damage, activations of WBC, PLT, and coagulation system, and hemolysis may terminate with chronic capillary endothelial damage, edema, and fibrosis (132). Stroke may not have a macrovascular origin, and an acute onset diffuse capillary endothelial edema may be much more important in the SCD. Therefore permanent neurological deficits are rare with stroke in the SCD. Infection, inflammation, medical or surgical emergency, and emotional stress may cause stroke by increasing basal metabolic rate and sickling. Low risk of stroke with hydroxyurea can also suggest that a significant proportion of stroke is developed due to the increased WBC and PLT counts-induced an acute capillary endothelial edema (133).

Acarbose is a pseudotetrasaccharide produced as a natural microbial product of Actinoplanes strain SE 50. It binds to oligosaccharide binding site of alpha-glucosidase enzymes in the brush border of the small intestinal mucosa with a dose-dependent manner, reversibly and competitively. It inhibits glycoamylase, sucrase, maltase, dextranase, and pancreatic alpha-amylase. It has little affinity for isomaltase but does not have any effect on beta-glucosidases such as lactase. By this way, it delays the intestinal hydrolysis of oligo- and disaccharides mainly in the upper half of the small intestine. As a result, the absorption of monosaccharides is delayed, and transport into the circulation is interrupted. Its effects may prolong up to 5 hours. The suppression of alpha-glucosidases is persistent with long-term use. Its usage results with carbohydrates appearing in the colon where bacterial fermentation occurs, and causes flatulence, loose stool, and abdominal discomfort (134). If started with a lower dosage and titrated slowly, side effects are tolerable (135). Long-term use increases colonic bacterial mass that of lactobacteria in particular. The finally impaired carbohydrate absorption, increased bacterial carbohydrate fermentation, and fecal acidification mimic effects of lactulose in portosystemic encephalopathy. So acarbose has a favourable therapeutic profile for the long-term use even in cirrhosis. Similarly, observed changes in bacterial flora and decreased stool pH and beta-hydroxybutyrate may be associated with anti-proliferative effects on the epithelial cells of colon that may potentially decrease carcinogenesis. After oral administration, less than 2% of the unchanged drug enters into the circulation. Therefore there is no need for dosage adjustment in mild renal insufficiency. After a high carbohydrate meal, acarbose lowers the postprandial rise in blood glucose by 20% and secondarily FPG by 15% (136). The initial improvement in blood glucose tends to be modest, but efficacy steadily improves with the long-term use. Its beneficial effects on serum lipids were also seen with a dose-dependent manner (136), because dietary carbohydrates are key precursors of lipogenesis, and insulin plays a central role for postprandial lipid metabolism. Carbohydrate-induced postprandial triglycerides synthesis is reduced for several hours, so acarbose lowers plasma triglycerides levels (136). The same beneficial effect is also seen in non-diabetic patients with hypertriglyceridemia, and acarbose reduced LDL significantly, and HDL remained as unchanged in hyperinsulinemic and overweight patients with impaired glucose tolerance (IGT) (137). Significantly elevated ursocholic acids in the stool appear to be the

additive endpoint of a decreased rate of absorption and increased intestinal motility due to the changes of intestinal flora. Acarbose may lower LDL via increased fecal bifido bacteria and biliary acids. Acarbose together with insulin was identified to be associated with a greater improvement in the oxidative stress and inflammation in DM (138). Probably, acarbose improves release of glucagon-like peptide-1, inhibits PLT activation, increases epithelial nitrous oxide synthase activity and nitrous oxide concentrations, promotes weight loss, decreases BP, and eventually prevents endothelial dysfunction (136). So it prevents atherosclerotic endpoints of excess fat tissue even in the absence of IGT or DM (139, 140). Although some authors reported as opposite (141), it should be used as the first-line antidiabetic agent. Based on more than 40 years of use, numerous studies did not show any significant side effect or toxicity (142). Although 25.9% of patients stopped metformin due to excessive anorexia (143), only 10.6% stopped acarbose due to an excessive flatulence or loose stool (144).

Metformin is a biguanide, and it is not metabolized, and 90% of absorbed drug is eliminated as unchanged in the urine. Plasma protein binding is negligible, so the drug is dialyzable. According to literature, antihyperglycemic effect of metformin is largely caused by inhibition of hepatic gluconeogenesis, increased insulin-mediated glucose disposal, inhibition of fatty acid oxidation, and reduction of intestinal glucose absorption (145, 146). Precise mechanism of intracellular action of metformin remains as unknown. Interestingly, 25.9% of patients stopped metformin due to the excessively lost appetite (143). Additionally, 14.1% of patients with overweight or obesity in the metformin group rose either to normal weight or overweight group by weight loss without a diet regimen (143). According to our opinion, the major effect of metformin is an inhibition of appetite. Similar results indicating the beneficial effects on the BMI, BP, FPG, and lipids were also reported (147, 148). Probably the major component of the metabolic syndrome may be the excess fat tissue. So treatment of excess fat tissue with acarbose plus metformin will probably prevent not only IGT or DM but also the other atherosclerotic endpoints.

As a conclusion, hardened RBC-induced capillary endothelial damage terminates with end-organ insufficiencies in early decades of life in SCD. Although atherosclerotic endpoints are so common, we detected no case of DM probably due to lower excess fat tissue. As the most common cause of CRD, DM may be a relative insufficiency of pancreas against the excess fat tissue. Increased blood and insulin requirements of excess fat in contrast to decreased blood supply of excess tissue and pancreas both due to excess external pressure and internal narrowing of vasculature may be important for DM. As the most common cause of DM, obesity may be an irreversible atherosclerotic endpoint in human body. Acarbose and metformin are oral, safe, cheap, and effective drugs to prevent obesity.

## References


1. Widlansky ME, Gokce N, Keaney JF Jr, Vita JA. The clinical implications of endothelial dysfunction. J Am Coll Cardiol 2003; 42(7): 1149-60.
2. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2005; 365(9468): 1415-28.
3. Franklin SS, Barboza MG, Pio JR, Wong ND. Blood pressure categories, hypertensive subtypes, and the metabolic syndrome. J Hypertens 2006; 24(10): 2009-16.
4. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002; 106(25): 3143-421.
5. Helvaci MR, Aydin LY, Aydin Y. Digital clubbing may be an indicator of systemic atherosclerosis even at microvascular level. HealthMED 2012; 6(12): 3977-81.
6. Anderson RN, Smith BL. Deaths: leading causes for 2001. Natl Vital Stat Rep 2003; 52(9): 1-85.
7. Helvaci MR, Gokce C, Davran R, Akkucuk S, Ugur M, Oruc C. Mortal quintet of sickle cell diseases. Int J Clin Exp Med 2015; 8(7): 11442-8.
8. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med 1994; 330(23): 1639-44.
9. Helvaci MR, Yaprak M, Abyad A, Pocock L. Atherosclerotic background of hepatosteatosis in sickle cell diseases. World Family Med 2018; 16(3): 12-8.
10. Helvaci MR, Kaya H. Effect of sickle cell diseases on height and weight. Pak J Med Sci 2011; 27(2): 361-4.
11. Helvaci MR, Aydin Y, Ayyildiz O. Hydroxyurea may prolong survival of sickle cell patients by decreasing frequency of painful crises. HealthMED 2013; 7(8): 2327-32.
12. Mankad VN, Williams JP, Harpen MD, Manci E, Longenecker G, Moore RB, et al. Magnetic resonance imaging of bone marrow in sickle cell disease: clinical, hematologic, and pathologic correlations. Blood 1990; 75(1): 274-83.
13. Helvaci MR, Aydin Y, Ayyildiz O. Clinical severity of sickle cell anemia alone and sickle cell diseases with thalassemias. HealthMED 2013; 7(7): 2028-33.
14. Fisher MR, Forfia PR, Chamera E, Housten-Harris T, Champion HC, Girgis RE, et al. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. Am J Respir Crit Care Med 2009; 179(7): 615-21.
15. Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2013; 187(4): 347-65.
16. Davies SC, Luce PJ, Win AA, Riordan JF, Brozovic M. Acute chest syndrome in sickle-cell disease. Lancet 1984; 1(8367): 36-8.

17. Vandemergel X, Renneboog B. Prevalence, aetiologies and significance of clubbing in a department of general internal medicine. Eur J Intern Med 2008; 19(5): 325-9.
18. Schamroth L. Personal experience. S Afr Med J 1976; 50(9): 297-300.
19. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med 1999; 341(15): 1097-105.
20. Helvaci MR, Aydin Y, Gundogdu M. Smoking induced atherosclerosis in cancers. HealthMED 2012; 6(11): 3744-9.
21. Ross R. Atherosclerosis--an inflammatory disease. N Engl J Med 1999; 340(2): 115-26.
22. Ridker PM. High-sensitivity C-reactive protein: Potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. Circulation 2001; 103(13): 1813-8.
23. Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. JAMA 1998; 279(18): 1477-82.
24. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. JAMA 1999; 282(22): 2131-5.
25. Zhou B, Wu Y, Yang J, Li Y, Zhang H, Zhao L. Overweight is an independent risk factor for cardiovascular disease in Chinese populations. Obes Rev 2002; 3(3): 147-56.
26. Zhou BF. Effect of body mass index on all-cause mortality and incidence of cardiovascular diseases--report for meta-analysis of prospective studies open optimal cut-off points of body mass index in Chinese adults. Biomed Environ Sci 2002; 15(3): 245-52.
27. Helvaci MR, Kaya H, Yalcin A, Kuvandik G. Prevalence of white coat hypertension in underweight and overweight subjects. Int Heart J 2007; 48(5): 605-13.
28. Heilbronn LK, Ravussin E. Calorie restriction and aging: review of the literature and implications for studies in humans. Am J Clin Nutr 2003; 78(3): 361-9.
29. Fodor JG, Tzerovska R, Dorner T, Rieder A. Do we diagnose and treat coronary heart disease differently in men and women? Wien Med Wochenschr 2004; 154(17-18): 423-5.
30. Helvaci MR, Aydin LY, Aydin Y. Chronic obstructive pulmonary disease may be one of the terminal end points of metabolic syndrome. Pak J Med Sci 2012; 28(3): 376-9.
31. Helvaci MR, Kayabasi Y, Celik O, Sencan H, Abyad A, Pocock L. Smoking causes a moderate or severe inflammatory process in human body. Am J Biomed Sci & Res 2023; 7(6): 694-702.
32. Grunberg NE, Greenwood MR, Collins F, Epstein LH, Hatsukami D, Niaura R, et al. National working conference on smoking and body weight. Task Force 1: Mechanisms relevant to the relations between cigarette smoking and body weight. Health Psychol 1992; 11: 4-9.
33. Helvaci MR, Camci C, Nisa EK, Ersahin T, Atabay A, Alrawii I, Ture Y, Abyad A, Pocock L. Severity of sickle cell diseases restricts smoking. Ann Med Medical Res 2024; 7: 1074.
34. Walker JF, Collins LC, Rowell PP, Goldsmith LJ, Moffatt RJ, Stamford BA. The effect of smoking on energy expenditure and plasma catecholamine and nicotine levels during light physical activity. Nicotine Tob Res 1999; 1(4): 365-70.
35. Hughes JR, Hatsukami DK. Effects of three doses of transdermal nicotine on post-cessation eating, hunger and weight. J Subst Abuse 1997; 9: 151-9.
36. Miyata G, Meguid MM, Varma M, Fetissov SO, Kim HJ. Nicotine alters the usual reciprocity between meal size and meal number in female rat. Physiol Behav 2001; 74(1-2): 169-76.
37. Froom P, Melamed S, Benbassat J. Smoking cessation and weight gain. J Fam Pract 1998; 46(6): 460-4.
38. Helvaci MR, Kaya H, Gundogdu M. Gender differences in coronary heart disease in Turkey. Pak J Med Sci 2012; 28(1): 40-4.
39. Prescott E, Hippe M, Schnohr P, Hein HO, Vestbo J. Smoking and risk of myocardial infarction in women and men: longitudinal population study. BMJ 1998; 316(7137): 1043-7.
40. Helvaci MR, Kabay S, Gulcan E. A physiologic events' cascade, irritable bowel syndrome, may even terminate with urolithiasis. J Health Sci 2006; 52(4): 478-81.
41. Helvaci MR, Dede G, Yildirim Y, Salaz S, Abyad A, Pocock L. Smoking may even cause irritable bowel syndrome. World Family Med 2019; 17(3): 28-33.
42. Helvaci MR, Algin MC, Kaya H. Irritable bowel syndrome and chronic gastritis, hemorrhoid, urolithiasis. Eurasian J Med 2009; 41(3): 158-61.
43. Kamimura D, Loprinzi PD, Wang W, Suzuki T, Butler KR, Mosley TH, et al. Physical activity is associated with reduced left ventricular mass in obese and hypertensive African Americans. Am J Hypertens 2017; 30(6): 617-23.
44. Sun Z, Lazar MA. Dissociating fatty liver and diabetes. Trends Endocrinol Metab 2013; 24(1): 4-12.
45. Rastogi A, Sakhuja P, Kumar A, Hissar S, Jain A, Gondal R, et al. Steatosis in chronic hepatitis B: prevalence and correlation with biochemical, histologic, viral, and metabolic parameters. Indian J Pathol Microbiol 2011; 54(3): 454-9.
46. Köse D, Erol C, Kaya F, Koplay M, Köksal Y. Development of fatty liver in children with non-Hodgkin lymphoma. Turk J Pediatr 2014; 56(4): 399-403.
47. Aktas E, Uzman M, Yildirim O, Sahin B, Buyukcam F, Aktas B, et al. Assessment of hepatic steatosis on contrast enhanced computed tomography in patients with colorectal cancer. Int J Clin Exp Med 2014; 7(11): 4342-6.
48. Balcik OS, Akdeniz D, Cipil H, Ikizek M, Uysal S, Kosar A, et al. Serum thrombopoietin levels in patients with non-alcoholic fatty liver disease. Saudi Med J 2012; 33(1): 30-3.
49. Çiftci A, Yilmaz B, Köklü S, Yüksel O, Özsoy M, Erden G, et al. Serum levels of nitrate, nitrite and advanced oxidation protein products (AOPP) in patients with nonalcoholic fatty liver disease. Acta Gastroenterol Belg 2015; 78(2): 201-5.

50. Kucukazman M, Ata N, Yavuz B, Dal K, Sen O, Deveci OS, et al. Evaluation of early atherosclerosis markers in patients with nonalcoholic fatty liver disease. Eur J Gastroenterol Hepatol 2013; 25(2): 147-51.
51. Agaç MT, Korkmaz L, Cavusoglu G, Karadeniz AG, Agaç S, Bektas H, et al. Association between nonalcoholic fatty liver disease and coronary artery disease complexity in patients with acute coronary syndrome: a pilot study. Angiology 2013; 64(8): 604-8.
52. Inci MF, Özkan F, Ark B, Vurdem ÜE, Ege MR, Sincer I, et al. Sonographic evaluation for predicting the presence and severity of coronary artery disease. Ultrasound Q 2013; 29(2): 125-30.
53. Öztürk H, Gümrükçüoğlu HA, Yaman M, Akyol A, Öztürk Ş, Akdağ S, et al. Hepatosteatosis and carotid intima-media thickness in patients with myocardial infarction. J Med Ultrason (2001) 2016; 43(1): 77-82.
54. Karasin M, Tokgoz O, Serifoglu I, Oz I, Erdem O. The Doppler ultrasonographic evaluation of hemodynamic changes in hepatic vascular structures in patients with hepatosteatosis. Pol J Radiol 2014; 79: 299-304.
55. Ozbulbul NI, Yurdakul M, Tola M. Does the visceral fat tissue show better correlation with the fatty replacement of the pancreas than with BMI? Eurasian J Med 2010; 42(1): 24-7.
56. Van Geenen EJ, Smits MM, Schreuder TC, van der Peet DL, Bloemena E, Mulder CJ. Nonalcoholic fatty liver disease is related to nonalcoholic fatty pancreas disease. Pancreas 2010; 39(8): 1185-90.
57. Stamm BH. Incidence and diagnostic significance of minor pathologic changes in the adult pancreas at autopsy: a systematic study of 112 autopsies in patients without known pancreatic disease. Hum Pathol 1984; 15(7): 677-83.
58. Lameloise N, Muzzin P, Prentki M, Assimacopoulos-Jeannet F. Uncoupling protein 2: a possible link between fatty acid excess and impaired glucose-induced insulin secretion? Diabetes 2001; 50(4): 803-9.
59. Aubert A, Garnet JM, Hammel P, Levy P, O'Toole D, Ruszniewski P, et al. Diffuse primary fat replacement of the pancreas: an unusual cause of steatorrhea. Gastroenterol Clin Biol 2007; 31(3): 303-6.
60. Chai J, Liu P, Jin E, Su T, Zhang J, Shi K, et al. MRI chemical shift imaging of the fat content of the pancreas and liver of patients with type 2 diabetes mellitus. Exp Ther Med 2016; 11(2): 476-80.
61. Quintero JHR, Grosser R, Velez GR, Ramos-Santillan VO, Pereira X, Flores FM, et al. Safety and efficacy of roux-en-y gastric bypass in older aged patients. Rev Col Bras Cir 2022; 49: e20223332.
62. Kim MK, Chun HJ, Park JH, Yea DM, Baek KH, Song KH, et al. The association between ectopic fat in the pancreas and subclinical atherosclerosis in type 2 diabetes. Diabetes Res Clin Pract 2014; 106(3): 590-6.
63. Selim Kul, Ayşegül Karadeniz, İhsan Dursun, Sinan Şahin, Ömer Faruk Çırakoğlu, Muhammet Raşit Sayın, et al. Non-Alcoholic Fatty Pancreas Disease is associated with Increased Epicardial Adipose Tissue and Aortic Intima-Media Thickness. Acta Cardiol Sin 2019; 35(2): 118-25.
64. Pezzilli R, Calculli L. Pancreatic steatosis: Is it related to either obesity or diabetes mellitus? World J Diabetes 2014; 5(4): 415-9.
65. Parfrey NA, Moore W, Hutchins GM. Is pain crisis a cause of death in sickle cell disease? Am J Clin Pathol 1985; 84(2): 209-12.
66. Helvaci MR, Ayyildiz O, Gundogdu M. Hydroxyurea therapy and parameters of health in sickle cell patients. HealthMED 2014; 8(4): 451-6.
67. Helvaci MR, Tonyali O, Yaprak M, Abyad A, Pocock L. Increased sexual performance of sickle cell patients with hydroxyurea. World Family Med 2019; 17(4): 28-33.
68. Helvaci MR, Aydin Y, Aydin LY, Sevinc A, Camci C, Abyad A, Pocock L. Red blood cell transfusions should be preserved just for emergencies in sickle cell diseases. World Family Med 2025; 23(4): 40-53.
69. Helvaci MR, Atci N, Ayyildiz O, Muftuoglu OE, Pocock L. Red blood cell supports in severe clinical conditions in sickle cell diseases. World Family Med 2016; 14(5): 11-8.
70. Helvaci MR, Ayyildiz O, Gundogdu M. Red blood cell transfusions and survival of sickle cell patients. HealthMED 2013; 7(11): 2907-12.
71. Helvaci MR, Cayir S, Halici H, Sevinc A, Camci C, Abyad A, Pocock L. Red blood cell transfusions may have the strongest analgesic effect during acute painful crises in sickle cell diseases. Ann Clin Med Case Rep 2024; V13(12): 1-12.
72. Miller ST, Sleeper LA, Pegelow CH, Enos LE, Wang WC, Weiner SJ, et al. Prediction of adverse outcomes in children with sickle cell disease. N Engl J Med 2000; 342(2): 83-9.
73. Balkaran B, Char G, Morris JS, Thomas PW, Serjeant BE, Serjeant GR. Stroke in a cohort of patients with homozygous sickle cell disease. J Pediatr 1992; 120(3): 360-6.
74. Cole TB, Sprinkle RH, Smith SJ, Buchanan GR. Intravenous narcotic therapy for children with severe sickle cell pain crisis. Am J Dis Child 1986; 140(12): 1255-9.
75. Miller BA, Platt O, Hope S, Dover G, Nathan DG. Influence of hydroxyurea on fetal hemoglobin production in vitro. Blood 1987; 70(6): 1824-9.
76. Platt OS. Is there treatment for sickle cell anemia? N Engl J Med 1988; 319(22): 1479-80.
77. Helvaci MR, Aydogan F, Sevinc A, Camci C, Dilek I. Platelet and white blood cell counts in severity of sickle cell diseases. Pren Med Argent 2014; 100(1): 49-56.
78. Charache S. Mechanism of action of hydroxyurea in the management of sickle cell anemia in adults. Semin Hematol 1997; 34(3): 15-21.
79. Charache S, Barton FB, Moore RD, Terrin ML, Steinberg MH, Dover GJ, et al. Hydroxyurea and sickle cell anemia. Clinical utility of a myelosuppressive "switching" agent. The Multicenter Study of Hydroxyurea in Sickle Cell Anemia. Medicine (Baltimore) 1996; 75(6): 300-26.
80. Steinberg MH, Barton F, Castro O, Pegelow CH, Ballas SK, Kutlar A, et al. Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment. JAMA 2003; 289(13): 1645-51.

81. Lebensburger JD, Miller ST, Howard TH, Casella JF, Brown RC, Lu M, et al; BABY HUG Investigators. Influence of severity of anemia on clinical findings in infants with sickle cell anemia: analyses from the BABY HUG study. Pediatr Blood Cancer 2012; 59(4): 675-8.
82. Toghi H, Konno S, Tamura K, Kimura B, Kawano K. Effects of low-to-high doses of aspirin on platelet aggregability and metabolites of thromboxane A2 and prostacyclin. Stroke 1992; 23(10): 1400-3.
83. Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009; 373(9678): 1849-60.
84. Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. Lancet Oncol 2012; 13(5): 518-27.
85. Macdonald S. Aspirin use to be banned in under 16 year olds. BMJ 2002; 325(7371): 988.
86. Schrör K. Aspirin and Reye syndrome: a review of the evidence. Paediatr Drugs 2007; 9(3): 195-204.
87. Pugliese A, Beltramo T, Torre D. Reye's and Reye's-like syndromes. Cell Biochem Funct 2008; 26(7): 741-6.
88. Hurwitz ES. Reye's syndrome. Epidemiol Rev 1989; 11: 249-53.
89. Meremikwu MM, Okomo U. Sickle cell disease. BMJ Clin Evid 2011; 2011: 2402.
90. Mohamed S, Fong CM, Ming YJ, Kori AN, Wahab SA, Ali ZM. Evaluation of an initiation regimen of warfarin for international normalized ratio target 2.0 to 3.0. J Pharm Technol 2021; 37(6): 286-92.
91. Chu MWA, Ruel M, Graeve A, Gerdisch MW, Ralph J, Damiano Jr RJ, Smith RL. Low-dose vs standard warfarin after mechanical mitral valve replacement: A randomized trial. Ann Thorac Surg 2023; 115(4): 929-38.
92. Crowther MA, Douketis JD, Schnurr T, Steidl L, Mera V, Ultori C, et al. Oral vitamin K lowers the international normalized ratio more rapidly than subcutaneously vitamin K in the treatment of warfarin-associated coagulopathy. A randomized, controlled trial. Ann Intern Med 2002; 137(4): 251-4.
93. Brown DG, Wilkerson EC, Love WE. A review of traditional and novel oral anticoagulant and antiplatelet therapy for dermatologists and dermatologic surgeons. J Am Acad Dermatol 2015; 72(3): 524-34.
94. Delaney JA, Opatrny L, Brophy JM, Suissa S. Drug drug interactions between antithrombotic medications and the risk of gastrointestinal bleeding. CMAJ 2007; 177(4): 347-51.
95. Dahal K, Kunwar S, Rijal J, Schulman P, Lee J. Stroke, major bleeding, and mortality outcomes in warfarin users with atrial fibrillation and chronic kidney disease: a meta-analysis of observational studies. Chest 2016; 149(4): 951-9.
96. Chai-Adisaksopha C, Lorio A, Hillis C, Siegal D, Witt DM, Schulman S, et al. Warfarin resumption following anticoagulant-associated intracranial hemorrhage: A systematic review and meta-analysis. Thromb Res 2017; 160: 97-104.
97. Ferro JM, Coutinho JM, Dentali F, Kobayashi A, Alasheev A, Canhao P, et al. Safety and efficacy of dabigatran etexilate vs dose-adjusted warfarin in patients with cerebral venous thrombosis: A randomized clinical trial. JAMA Neurol 2019; 76(12): 1457-65.
98. Meade TW. Low-dose warfarin and low-dose aspirin in the primary prevention of ischemic heart disease. Am J Cardiol 1990; 65(6): 7C-11C.
99. Singer DE, Hughes RA, Gress DR, Sheehan MA, Oertel LB, Maraventano SW, et al. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. N Engl J Med 1990; 323(22): 1505-11.
100. Levine M, Hirsh J, Gent M, Arnold A, Warr D, Falanya A, et al. Double-blind randomised trial of a very-low-dose warfarin for prevention of thromboembolism in stage IV breast cancer. Lancet 1994; 343(8902): 886-9.
101. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014; 383(9921): 955-62.
102. Vinogradova Y, Coupland C, Hill T, Hippisley-Cox J. Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care. BMJ 2018; 362: k2505.
103. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361(12): 1139-51.
104. Helvaci MR, Cayir S, Halici H, Sevinc A, Camci C, Abyad A, Pocock L. Terminal endpoints of systemic atherosclerotic processes in sickle cell diseases. World Family Med 2024; 22(5): 13-23.
105. Helvaci MR, Daglioglu MC, Halici H, Sevinc A, Camci C, Abyad A, Pocock L. Low-dose aspirin plus low-dose warfarin may be the standard treatment regimen in Buerger's disease. World Family Med 2024; 22(6): 22-35.
106. Helvaci MR, Erden ES, Aydin LY. Atherosclerotic background of chronic obstructive pulmonary disease in sickle cell patients. HealthMED 2013; 7(2): 484-8.
107. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. Lancet 2009; 374(9691): 733-43.
108. Schoepf D, Heun R. Alcohol dependence and physical comorbidity: Increased prevalence but reduced relevance of individual comorbidities for hospital-based mortality during a 12.5-year observation period in general hospital admissions in urban North-West England. Eur Psychiatry 2015; 30(4): 459-68.
109. Singh G, Zhang W, Kuo YF, Sharma G. Association of Psychological Disorders With 30-Day Readmission Rates in Patients With COPD. Chest 2016; 149(4): 905-15.
110. Mannino DM, Watt G, Hole D, Gillis C, Hart C, McConnachie A, et al. The natural history of chronic obstructive pulmonary disease. Eur Respir J 2006; 27(3): 627-43.
111.Mapel DW, Hurley JS, Frost FJ, Petersen HV, Picchi MA, Coultas DB. Health care utilization in chronic obstructive pulmonary disease. A case-control study in a health maintenance organization. Arch Intern Med 2000; 160(17): 2653-58.

112. Anthonisen NR, Connett JE, Enright PL, Manfreda J; Lung Health Study Research Group. Hospitalizations and mortality in the Lung Health Study. Am J Respir Crit Care Med 2002; 166(3): 333-9.
113. McGarvey LP, John M, Anderson JA, Zvarich M, Wise RA; TORCH Clinical Endpoint Committee. Ascertainment of cause-specific mortality in COPD: operations of the TORCH Clinical Endpoint Committee. Thorax 2007; 62(5): 411-5.
114. Trent JT, Kirsner RS. Leg ulcers in sickle cell disease. Adv Skin Wound Care 2004: 17(8); 410-6.
115. Minniti CP, Eckman J, Sebastiani P, Steinberg MH, Ballas SK. Leg ulcers in sickle cell disease. Am J Hematol 2010; 85(10): 831-3.
116. Yawn BP, Buchanan GR, Afenyi-Annan AN, Ballas SK, Hassell KL, James AH, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA 2014; 312(10): 1033-48.
117. Helvaci MR, Aydogan F, Sevinc A, Camci C, Dilek I. Platelet and white blood cell counts in severity of sickle cell diseases. HealthMED 2014; 8(4): 477-82.
118. Myers KA, Farquhar DR. The rational clinical examination. Does this patient have clubbing? JAMA 2001; 286(3): 341-7.
119. Toovey OT, Eisenhauer HJ. A new hypothesis on the mechanism of digital clubbing secondary to pulmonary pathologies. Med Hypotheses 2010; 75(6): 511-3.
120. Nassiri AA, Hakemi MS, Asadzadeh R, Faizei AM, Alatab S, Miri R, et al. Differences in cardiovascular disease risk factors associated with maximum and mean carotid intima-media thickness among hemodialysis patients. Iran J Kidney Dis 2012; 6(3): 203-8.
121. Helvaci MR, Gokce C, Sahan M, Hakimoglu S, Coskun M, Gozukara KH. Venous involvement in sickle cell diseases. Int J Clin Exp Med 2016; 9(6): 11950-7.
122. Xia M, Guerra N, Sukhova GK, Yang K, Miller CK, Shi GP, et al. Immune activation resulting from NKG2D/ligand interaction promotes atherosclerosis. Circulation 2011; 124(25): 2933-43.
123. Hall JE, Henegar JR, Dwyer TM, Liu J, da Silva AA, Kuo JJ, et al. Is obesity a major cause of chronic kidney disease? Adv Ren Replace Ther 2004; 11(1): 41-54.
124. Nerpin E, Ingelsson E, Risérus U, Helmersson-Karlqvist J, Sundström J, Jobs E, et al. Association between glomerular filtration rate and endothelial function in an elderly community cohort. Atherosclerosis 2012; 224(1): 242-6.
125. Stengel B, Tarver-Carr ME, Powe NR, Eberhardt MS, Brancati FL. Lifestyle factors, obesity and the risk of chronic kidney disease. Epidemiology 2003; 14(4): 479-87.
126. Bonora E, Targher G. Increased risk of cardiovascular disease and chronic kidney disease in NAFLD. Nat Rev Gastroenterol Hepatol 2012; 9(7): 372-81.
127. Helvaci MR, Cayir S, Halici H, Sevinc A, Camci C, Sencan H, Davran R, Abyad A, Pocock L. Acute chest syndrome and coronavirus disease may actually be genetically determined exaggerated immune response syndromes particularly in pulmonary capillaries. World Family Med 2024; 22(3): 6-16.
128. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, et al. Chronic kidney disease and mortality risk: a systematic review. J Am Soc Nephrol 2006; 17(7): 2034-47.
129. Helvaci MR, Aydin Y, Aydin LY. Atherosclerotic background of chronic kidney disease in sickle cell patients. HealthMED 2013; 7(9): 2532-7.
130. DeBaun MR, Gordon M, McKinstry RC, Noetzel MJ, White DA, Sarnaik SA, et al. Controlled trial of transfusions for silent cerebral infarcts in sickle cell anemia. N Engl J Med 2014; 371(8): 699-710.
131. Majumdar S, Miller M, Khan M, Gordon C, Forsythe A, Smith MG, et al. Outcome of overt stroke in sickle cell anaemia, a single institution's experience. Br J Haematol 2014; 165(5): 707-13.
132. Kossorotoff M, Grevent D, de Montalembert M. Cerebral vasculopathy in pediatric sickle-cell anemia. Arch Pediatr 2014; 21(4): 404-14.
133. Charache S, Terrin ML, Moore RD, Dover GJ, Barton FB, Eckert SV, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. N Engl J Med 1995; 332(20): 1317-22.
134. Rosak C, Mertes G. Critical evaluation of the role of acarbose in the treatment of diabetes: patient considerations. Diabetes Metab Syndr Obes 2012; 5: 357-67.
135. Salvatore T, Giugliano D. Pharmacokinetic-pharmacodynamic relationships of acarbose. Clin Pharmacokinet 1996; 30(2): 94-106.
136. DiNicolantonio JJ, Bhutani J, O'Keefe JH. Acarbose: safe and effective for lowering postprandial hyperglycaemia and improving cardiovascular outcomes. Open Heart 2015; 2(1): e000327.
137. Leonhardt W, Hanefeld M, Fischer S, Schulze J. Efficacy of alpha-glucosidase inhibitors on lipids in NIDDM subjects with moderate hyperlipidaemia. Eur J Clin Invest 1994; 24(3): 45-9.
138. Li FF, Fu LY, Xu XH, Su XF, Wu JD, Ye L, et al. Analysis of the add-on effect of alpha-glucosidase inhibitor, acarbose in insulin therapy: A pilot study. Biomed Rep 2016; 5(4): 461-6.
139. Standl E, Schnell O, Ceriello A. Postprandial hyperglycemia and glycemic variability: should we care? Diabetes Care 2011; 34(2): 120-7.
140. Helvaci MR, Halici H, Erdogan K, Sevinc A, Camci C, Abyad A, Pocock L. Acarbose in the treatment of chronic obstructive pulmonary disease. World Family Med 2025; 23(2): 37-52.
141. Wettergreen SA, Sheth S, Malveaux J. Effects of the addition of acarbose to insulin and non-insulin regimens in veterans with type 2 diabetes mellitus. Pharm Pract (Granada) 2016; 14(4): 832.
142. Van De Laar FA, Lucassen PL, Akkermans RP, Van de Lisdonk EH, Rutten GE, Van Weel C. Alpha-glucosidase inhibitors for patients with type 2 diabetes: results from a Cochrane systematic review and meta-analysis. Diabetes Care 2005; 28(1): 154-63.
143. Helvaci MR, Kaya H, Borazan A, Ozer C, Seyhanli M, Yalcin A. Metformin and parameters of physical health. Intern Med 2008; 47(8): 697-703.

144. Helvaci MR, Aydin Y, Varan G, Abyad A, Pocock L. Acarbose versus metformin in the treatment of metabolic syndrome. World Family Med 2018; 16(5): 10-15.
145. Stumvoll M, Nurjhan N, Perriello G, Dailey G, Gerich JE. Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. N Engl J Med 1995; 333(9): 550-554.
146. Jackson RA, Hawa MI, Jaspan JB, Sim BM, Disilvio L, Featherbe D, et al. Mechanism of metformin action in non-insulin-dependent diabetes. Diabetes 1987; 36(5): 632-640.
147. Campbell IW, Howlett HC. Worldwide experience of metformin as an effective glucose-lowing agent: a meta-analysis. Diabetes Metab Rev 1995; 11(1): 57-62.
148. Helvaci MR, Kurt GD, Halici H, Sevinc A, Camci C, Abyad A, Pocock L. Metformin in the treatment of chronic renal disease. World Family Med 2025; 23(1): 12-27.

# Vascular Dementia: Cerebrovascular Injury, Clinical Syndromes, Neuroimaging, and Interaction with Alzheimer Pathology

A. Abyad

**Correspondence**
A. Abyad, MD, MPH, MBA, DBA, AGSF
Consultant, Internal Medicine and Geriatric, Dar Al Shifa Hospital, Kuwait
Chairman, Middle-East Academy for Medicine of Aging.
President, Middle East & North Africa Association on Aging & Alzheimer's
Coordinator, Middle-East Primary Care Research Network
Coordinator, Middle-East Network on Aging
**Email:** aabyad@cyberia.net.lb

Received: November 2025. Accepted: December 2025; Published: January/February 2026.
Citation: Abyad A. Vascular Dementia: Cerebrovascular Injury, Clinical Syndromes, Neuroimaging, and Interaction with Alzheimer Pathology. World Family Medicine. January/February 2026; 24(1): 22 - 38. DOI: 10.5742/MEWFM.2026.2401022

## Abstract

Vascular dementia (VaD) represents a heterogeneous group of cognitive disorders caused by cerebrovascular disease and remains the second most common cause of dementia worldwide after Alzheimer's disease. Rather than a single disease entity, VaD encompasses multiple pathophysiological mechanisms, including large-vessel infarction, small-vessel disease, strategic infarcts, hypoperfusion-related injury, and hemorrhagic lesions. Advances in neuroimaging and neuropathology have refined the understanding of how cerebrovascular injury disrupts distributed neural networks, leading to executive dysfunction, slowed processing speed, and impaired attention that distinguish VaD from primary neurodegenerative dementias. Increasingly, evidence demonstrates that vascular pathology rarely occurs in isolation; instead, mixed dementia, particularly the coexistence of vascular brain injury with Alzheimer-type pathology, is the most common substrate underlying late-life cognitive impairment.

This narrative review provides a comprehensive synthesis of updated literature on vascular dementia, focusing on types of cerebrovascular injury, clinical syndromes, neuroimaging correlates, and interactions with Alzheimer pathology. Emphasis is placed on mechanistic pathways, clinico-radiologic correlations, and implications for diagnosis, prognosis and prevention.

Key words:
Vascular dementia, cerebrovascular injury, clinical syndromes, neuroimaging, Alzheimer pathology

## Introduction

Dementia is a leading cause of disability and dependency among older adults, with substantial societal and economic impact. Vascular dementia (VaD) has historically been conceptualized as a consequence of cumulative ischemic brain injury resulting from cerebrovascular disease. However, this traditional view has evolved significantly over the past two decades. Contemporary research highlights the complexity of vascular contributions to cognitive impairment, recognizing VaD as a spectrum disorder with diverse etiologies, clinical presentations, and pathological substrates (O'Brien & Thomas, 2015; Skrobot et al., 2018).

Epidemiological studies suggest that purely "vascular-only" dementia is relatively uncommon, particularly in older populations. Instead, mixed dementia—characterized by the coexistence of vascular brain injury and Alzheimer pathology—accounts for a substantial proportion of cases (Schneider et al., 2007; Toledo et al., 2013). This overlap has important implications for diagnosis, clinical management, and research, as vascular pathology may lower the threshold at which Alzheimer pathology becomes clinically manifest.

Recognition of vascular contributions to cognitive impairment has expanded beyond overt infarction to include small-vessel disease, white matter injury, cerebral microbleeds, blood–brain barrier dysfunction, and chronic hypoperfusion. These processes preferentially affect frontal–subcortical circuits, resulting in characteristic patterns of cognitive impairment that distinguish VaD from Alzheimer's disease (AD), although overlap is common (Roman et al., 1993; Sachdev et al., 2014).

This review synthesizes current knowledge on VaD, with particular focus on cerebrovascular injury types, clinical syndromes, neuroimaging findings, and interaction with Alzheimer pathology.

## Conceptual Framework and Definitions

**1. Evolution of the Concept of Vascular Dementia**

The term "vascular dementia" was initially used to describe dementia resulting from multiple cortical infarcts, often with a stepwise clinical course. Early diagnostic criteria emphasized abrupt onset, focal neurological signs, and temporal association with stroke events (Hachinski et al., 1974). While useful, this framework underestimated the contribution of subclinical vascular injury and small-vessel disease.

Subsequent diagnostic systems broadened the definition to include subcortical ischemic vascular dementia, strategic infarct dementia, and hypoperfusion-related cognitive impairment (Roman et al., 1993). More recently, the concept of vascular cognitive impairment (VCI) has been introduced to encompass the full spectrum of cognitive dysfunction attributable to cerebrovascular disease, ranging from mild cognitive impairment to overt dementia (Sachdev et al., 2014).

**2. Vascular Cognitive Impairment Continuum**

VCI emphasizes that cognitive impairment due to vascular causes exists along a continuum rather than as a dichotomous state. Mild cognitive deficits may precede dementia by years and offer opportunities for intervention through vascular risk factor modification (Gorelick et al., 2011).

**Table 1. Spectrum of Vascular Cognitive Impairment**

| Stage | Description | Clinical Features |
|---|---|---|
| Vascular brain injury without cognitive impairment | Imaging evidence of infarcts or white matter disease | No functional impact |
| Vascular mild cognitive impairment | Measurable cognitive decline | Preserved activities of daily living |
| Vascular dementia | Cognitive impairment with functional decline | Loss of independence |

This framework underscores the importance of early detection and prevention.

## Types of Cerebrovascular Injury in Vascular Dementia

Cerebrovascular injury in VaD arises from multiple mechanisms, often coexisting within the same individual. The type, location, and cumulative burden of vascular lesions determine clinical expression (Pantoni, 2010).

**1. Large-Vessel Ischemic Infarction**
Large-vessel disease leads to cortical or cortico-subcortical infarcts due to atherosclerosis or cardioembolism. Cognitive impairment results when infarcts involve association cortices or when multiple lesions disrupt distributed networks (Bowler et al., 1997).

Large territorial infarcts may produce acute cognitive decline, whereas multiple smaller infarcts accumulate over time, leading to progressive deterioration.

**2. Small-Vessel Disease**
Small-vessel disease (SVD) is the most common pathological substrate of VaD. It affects penetrating arterioles and capillaries, leading to lacunar infarcts, white matter hyperintensities, microinfarcts, and microbleeds (Pantoni, 2010). Risk factors include hypertension, diabetes, aging, and genetic susceptibility. SVD preferentially damages frontal–subcortical circuits, producing executive dysfunction and psychomotor slowing (Prins & Scheltens, 2015).

**3. Strategic Infarcts**
Strategic infarct dementia results from single lesions in cognitively critical regions such as the thalamus, hippocampus, angular gyrus, basal forebrain, or caudate nucleus. Despite limited lesion volume, disruption of key hubs can cause disproportionate cognitive deficits (Ghika-Schmid & Bogousslavsky, 2000).

**4. Chronic Hypoperfusion and Border-Zone Injury**
Chronic cerebral hypoperfusion, often due to cardiac failure or severe carotid disease, contributes to diffuse white matter injury and cortical dysfunction. Border-zone infarcts between major arterial territories are particularly vulnerable (De la Torre, 2012).

**5. Hemorrhagic and Microvascular Injury**
Cerebral microbleeds and hemorrhages, frequently associated with cerebral amyloid angiopathy or hypertensive arteriopathy, contribute to cognitive decline through direct tissue injury and network disruption (Greenberg et al., 2009).

**Table 2. Major Types of Cerebrovascular Injury in VaD**

| Injury Type | Typical Lesions | Cognitive Impact |
|---|---|---|
| Large-vessel infarction | Cortical infarcts | Aphasia, visuospatial deficits |
| Small-vessel disease | Lacunes, WMH | Executive dysfunction |
| Strategic infarcts | Thalamus, hippocampus | Memory, attention deficits |
| Hypoperfusion | Border-zone lesions | Global slowing |
| Hemorrhagic injury | Microbleeds | Executive and attentional deficits |

## Clinical Syndromes of Vascular Dementia (Overview)

Vascular dementia presents with heterogeneous clinical syndromes reflecting underlying vascular pathology. Unlike Alzheimer's disease, early memory impairment is often less prominent, while executive dysfunction, slowed processing speed, and attentional deficits are characteristic (O'Brien & Thomas, 2015).

The major clinical syndromes include:

- Multi-infarct dementia
- Strategic infarct dementia
- Subcortical ischemic vascular dementia (small-vessel disease)

These syndromes frequently overlap, particularly in older adults with mixed pathology.

## Clinical Syndromes of Vascular Dementia

Vascular dementia (VaD) is best understood as a set of clinical syndromes arising from different patterns of cerebrovascular injury. Contemporary frameworks increasingly use the umbrella term vascular cognitive impairment and dementia (VCID) to emphasize that cognitive impairment due to vascular disease spans from mild impairment to major neurocognitive disorder and often coexists with neurodegenerative pathology (Sachdev et al., 2025). In geriatric practice, differentiating clinical syndromes is valuable for prognosis and for aligning neuroimaging findings with plausible mechanisms of cognitive decline (Ng & colleagues, 2025; Mok et al., 2024).

Across syndromes, VaD typically features disproportionate impairment in processing speed, attention, executive function, and gait/psychomotor features, reflecting disruption of frontal–subcortical networks and white matter connectivity; memory impairment may be present but is often less prominent early than in typical Alzheimer presentations (Mok et al., 2024; Duering et al., 2023). Syndrome boundaries are imperfect because mixed lesion patterns are common, particularly in late life (Ng & colleagues, 2025).

**Table 3. Core Clinical Syndrome Patterns in VaD (Practical, Clinic-Oriented)**

| Syndrome | Typical Course | Core Cognitive Profile | Common Associated Features |
|---|---|---|---|
| **Multi-infarct (cortical) dementia** | Stepwise or fluctuating, often post-stroke | Variable; may include language/visuospatial deficits | Focal neurological signs; stroke history |
| **Strategic infarct dementia** | Abrupt or subacute after a single lesion | Domain-specific deficits (memory/attention/ executive) | Focal deficits depending on lesion site |
| **Subcortical ischemic VaD (small vessel disease)** | Insidious, slowly progressive | Processing speed/executive dysfunction > memory | Gait disorder, falls, mood changes, urinary symptoms |

(Updated syndrome framing and clinicoradiologic emphasis: Ng & colleagues, 2025; Mok et al., 2024; Duering et al., 2023)

**1 Multi-Infarct Dementia (Cortical and Cortico-Subcortical Infarction)**

***Clinical features and trajectory***

Multi-infarct dementia traditionally describes cognitive impairment attributable to multiple ischemic infarcts, often in a stepwise manner following clinically overt strokes. Modern practice recognizes that the “stepwise” pattern is not mandatory; multi-infarct presentations can be progressive, particularly when recurrent silent infarcts occur or when coexisting small vessel disease adds a chronic burden of white matter injury (Ng & colleagues, 2025).

The cognitive profile depends on lesion distribution. Cortical infarcts affecting language networks can produce aphasia-dominant decline, while parietal or posterior lesions can generate visuospatial deficits and apraxias. When infarcts are dispersed across multiple networks, the result may be global cognitive impairment with prominent executive deficits and impaired attention (Mok et al., 2024).

Recent syntheses emphasize the importance of quantifying lesion burden and network disruption, rather than counting discrete infarcts. Neuroimaging phenotype approaches are increasingly used in research to link patterns of infarction to cognitive outcomes and dementia risk (Chen et al., 2025). Similarly, the field has pushed toward standardized neuropsychological domain mapping to improve diagnostic reliability in VCID (Bentvelzen et al., 2025; Sachdev et al., 2025).

**Table 4. Multi-Infarct Dementia: High-Yield Clinical and Imaging Correlates**

| Feature | Clinical expression | Typical neuroimaging correlate |
|---|---|---|
| Post-stroke cognitive decline | Decline after index stroke | Territorial infarct(s), cortical involvement |
| Recurrent vascular events | Stepwise or episodic deterioration | Multiple infarcts over time, new DWI lesions |
| Network disruption | Executive/attention impairment | Distributed infarcts, reduced connectivity |
| Coexisting SVD | Slower progression, gait involvement | WMH, lacunes, microbleeds alongside infarcts |

(Phenotype-based and standardized assessment emphasis: Chen et al., 2025; Bentvelzen et al., 2025; Duering et al., 2023; Ng & colleagues, 2025)

**2 Strategic Infarct Dementia**

***Concept***

Strategic infarct dementia refers to dementia or major cognitive impairment resulting from a single infarct in a cognitively critical "hub" region or connecting pathway, where lesion location outweighs lesion volume. Updated clinical reviews stress that strategic lesions can be cortical or subcortical and may produce abrupt or rapidly evolving cognitive syndromes (Ng & colleagues, 2025).

***Key lesion locations and clinical syndromes***

Strategic lesions commonly involve:

- Thalamus (attention, arousal, memory circuitry)
- Basal forebrain (cholinergic projections to cortex)
- Hippocampus/medial temporal structures (memory encoding)
- Angular gyrus/posterior association cortex (language/semantic integration)
- Caudate and frontal-subcortical circuits (executive function and motivation)

Clinically, patients may present with prominent attentional deficits, dysexecutive syndrome, apathy, memory impairment, or language dysfunction depending on lesion site. Because older adults frequently have silent comorbid small-vessel disease or Alzheimer pathology, determining causality requires careful temporal correlation between infarct timing and cognitive decline, supported by imaging (Sachdev et al., 2025; Ng & colleagues, 2025).

**Table 5. Strategic Infarct Locations and Typical Cognitive Presentations**

| Strategic region | Typical cognitive phenotype | Common clinical clues |
|---|---|---|
| Thalamus | Attention/executive dysfunction, memory retrieval problems | Somnolence, fluctuating attention |
| Basal forebrain | Prominent amnestic syndrome, attentional deficits | Abrupt memory decline, apathy |
| Caudate/frontal-subcortical circuits | Dysexecutive syndrome, slowed processing | Apathy, reduced initiative, gait issues |
| Angular gyrus/parietal association | Language, calculation, visuospatial deficits | Alexia, acalculia, apraxia |
| Hippocampal/medial temporal infarct | Memory encoding impairment | Acute anterograde amnesia pattern |

(Clinical syndromes contextualized within updated VCID diagnostic logic: Sachdev et al., 2025; Ng & colleagues, 2025)

### 3 Subcortical Ischemic Vascular Dementia and Small Vessel Disease–Related VCID

***Why small vessel disease dominates late-life VCID***

Cerebral small vessel disease (cSVD) is now widely recognized as a primary driver of vascular cognitive impairment and a major contributor to dementia burden in aging populations (Duering et al., 2023; Hainsworth et al., 2024). cSVD produces chronic, cumulative injury—often "silent" clinically—manifesting as white matter disconnection, lacunes, microinfarcts, and microbleeds. This injury aligns with a clinical syndrome marked by slowed processing speed, impaired executive function, gait disturbance, mood symptoms, and urinary dysfunction (Mok et al., 2024; Markus, 2023).

***Updated standards: STRIVE-2 and imaging harmonization***

A major 2022–2025 advance has been the push for improved consistency in describing cSVD imaging features. Research standards have been updated since the original STRIVE recommendations, with emphasis on harmonized acquisition and reporting across studies and clinical trials (Duering et al., 2023). This standardization is critical because cSVD markers are used both for diagnosis and as surrogate outcomes in trials.

**Cognitive phenotype in cSVD-related VaD**

The neuropsychological pattern is often:

- Processing speed impairment (early and prominent)
- Executive dysfunction (planning, set-shifting, attention)
- Reduced mental flexibility
- Variable memory impairment (often retrieval rather than encoding early)

The syndrome may be subtle initially, making it clinically under-recognized unless structured cognitive testing is used. Recent consensus work has reinforced domain-based assessment in VCID and supports more standardized neuropsychological evaluation to improve diagnostic reliability across settings (Bentvelzen et al., 2025; Sachdev et al., 2025).

**Table 6. cSVD-Related VCID: Clinical Profile and Common Imaging Markers**

| Domain | Typical clinical finding | Imaging correlate |
|---|---|---|
| Executive function | Dysexecutive syndrome, reduced planning | WMH, lacunes, strategic subcortical lesions |
| Processing speed | Slowed thinking, psychomotor slowing | Diffuse WMH, microstructural damage |
| Gait/balance | Gait instability, falls | WMH burden, lacunes |
| Mood/behaviour | Apathy, depression | Frontal-subcortical disconnection |
| Vascular vulnerability | Fluctuating cognition with illness | Chronic cSVD + reduced reserve |

(Updated imaging/reporting and clinic mechanisms: Duering et al., 2023; Hainsworth et al., 2024; Mok et al., 2024; Markus, 2023)

**Total cSVD burden concepts (2024–2025)**

Recent studies and reviews increasingly use "total cSVD burden" scores, combining WMH, lacunes, microbleeds, and perivascular spaces to reflect cumulative injury. Systematic evaluation of these scores' reliability and validity is expanding, supporting their use in research and potentially in clinical stratification (Silva et al., 2025). This is aligned with the broader movement toward quantitative and harmonized cSVD characterization (Duering et al., 2023).

## Neuroimaging in Vascular Dementia: Introduction to the Diagnostic Role

Neuroimaging is central to modern diagnosis of VaD/VCID because it provides objective evidence of vascular brain injury, helps attribute causality, identifies mixed pathology patterns, and supports prognostication (Sachdev et al., 2025; Ng & colleagues, 2025). In clinical practice, MRI is preferred over CT because it better visualizes white matter hyperintensities, lacunes, microbleeds, and strategic infarcts that define syndromic subtypes (Duering et al., 2023; Mok et al., 2024).

**Table 7. Imaging Modalities and the VaD/VCID Questions they Answer**

| Modality | Strengths | Best for |
|---|---|---|
| MRI (FLAIR) | Sensitive to WMH | cSVD burden, disconnection patterns |
| MRI (DWI) | Detects acute/subacute ischemia | New infarcts, post-stroke cognition |
| MRI (SWI/T2*) | Sensitive to microbleeds | Hemorrhagic injury, amyloid angiopathy suspicion |
| CT | Rapid, accessible | Large infarcts/hemorrhage screening |

(Updated standards and diagnostic emphasis: Duering et al., 2023; Sachdev et al., 2025; Mok et al., 2024)

1. Neuroimaging findings in VaD/VCID (WMH patterns, lacunes, microbleeds, cortical infarcts, strategic lesions, total cSVD burden) with multiple tables aligned to contemporary standards (Duering et al., 2023; Hainsworth et al., 2024; Silva et al., 2025).

2. Interaction with Alzheimer pathology (mixed dementia, amyloid angiopathy, vascular lowering of AD threshold, biomarker-era diagnostic framing), including how new AD biological criteria intersect with VCID frameworks (Alzheimer's Association workgroup, 2024; Sachdev et al., 2025).

## Neuroimaging Findings in Vascular Dementia

Neuroimaging is indispensable for the diagnosis and characterization of vascular dementia and vascular cognitive impairment and dementia (VCID). Contemporary diagnostic frameworks emphasize that cognitive symptoms must be plausibly attributable to vascular brain injury demonstrated on imaging, rather than inferred solely from vascular risk factors or clinical history (Sachdev et al., 2025). Magnetic resonance imaging (MRI) is the modality of choice, as it provides superior sensitivity for small-vessel disease markers, strategic infarcts, and hemorrhagic lesions that are central to VaD pathophysiology (Duering et al., 2023; Mok et al., 2024).

**1 White Matter Hyperintensities**

White matter hyperintensities (WMH), visible on T2-weighted and FLAIR MRI sequences, are the most common imaging abnormality in VaD. WMH reflect chronic ischemic injury, demyelination, axonal loss, and gliosis secondary to small-vessel disease. Recent longitudinal studies demonstrate that WMH burden and progression are strongly associated with executive dysfunction, slowed processing speed, gait impairment, and incident dementia (Hainsworth et al., 2024; Mok et al., 2024).

Importantly, WMH location matters. Periventricular and deep frontal WMH disrupt long-range association fibers and fronto-subcortical circuits, producing the characteristic dysexecutive phenotype seen in subcortical ischemic VaD. Posterior WMH are more strongly associated with visuospatial dysfunction and may overlap with Alzheimer-related processes (Duering et al., 2023).

**2 Lacunar Infarcts and Subcortical Lesions**

Lacunar infarcts are small (<15 mm) cavities resulting from occlusion of penetrating arterioles. Although individually small, their cumulative effect can be substantial. Recent imaging-pathology correlation studies show that lacunes frequently coexist with diffuse microstructural white matter damage that is not fully captured by conventional MRI, further amplifying cognitive impact (Duering et al., 2023; Markus, 2023).

Clinically, lacunes are associated with executive dysfunction, attention deficits, and gait abnormalities. Thalamic and basal ganglia lacunes are particularly impactful due to their role in cognitive network integration (Mok et al., 2024).

**3 Cerebral Microbleeds and Hemorrhagic Injury**

Cerebral microbleeds (CMBs), detected on susceptibility-weighted imaging (SWI) or T2*-weighted MRI, reflect hemosiderin deposition from prior microscopic hemorrhage. Their distribution provides important etiologic clues. Deep and infratentorial microbleeds are typically associated with hypertensive arteriopathy, whereas lobar microbleeds suggest cerebral amyloid angiopathy (CAA) (Greenberg et al., 2009; Charidimou et al., 2022).

Recent studies demonstrate that microbleed burden is independently associated with cognitive decline, particularly in executive and attentional domains, and increases the risk of dementia progression in patients with mixed vascular and Alzheimer pathology (Charidimou et al., 2022; Silva et al., 2025).

**4 Strategic Infarcts on Neuroimaging**

Strategic infarcts may be subtle on imaging but have disproportionate cognitive consequences. Modern MRI allows precise localization of lesions affecting key nodes such as the thalamus, basal forebrain, hippocampus, caudate nucleus, and angular gyrus. Network-based imaging analyses increasingly show that disconnection of white matter tracts linking these hubs contributes as much to cognitive impairment as the focal lesion itself (Duering et al., 2023; Chen et al., 2025).

**Table 8. Key Neuroimaging Markers in VaD and Their Cognitive Correlates**

| Imaging marker | Typical MRI sequence | Cognitive domains affected |
|---|---|---|
| White matter hyperintensities | FLAIR | Executive function, processing speed |
| Lacunes | T1/T2 | Executive function, gait |
| Strategic infarcts | DWI/T1 | Domain-specific deficits |
| Microbleeds | SWI/T2* | Executive function, attention |
| Cortical infarcts | DWI/FLAIR | Language, visuospatial skills |

(Updated imaging-clinic correlations: Duering et al., 2023; Mok et al., 2024; Silva et al., 2025)

**5 Total Cerebral Small Vessel Disease Burden**

An important conceptual advance in recent years has been the shift from single-marker interpretation to total cSVD burden assessment. Composite scores incorporate WMH, lacunes, microbleeds, and enlarged perivascular spaces to represent cumulative vascular injury (Silva et al., 2025).

Studies from 2022–2025 show that higher total cSVD burden predicts faster cognitive decline, poorer functional outcomes, and greater dementia risk, even after adjusting for age and Alzheimer pathology biomarkers (Hainsworth et al., 2024; Silva et al., 2025). This approach aligns with the network-disruption model of VaD and supports its use in both research and clinical stratification.

## Interaction Between Vascular Dementia and Alzheimer Pathology

**1 Mixed Dementia as the Predominant Late-Life Phenotype**
Accumulating neuropathological and biomarker evidence indicates that pure vascular dementia is relatively uncommon in older adults. Instead, most individuals with late-life dementia exhibit mixed pathology, most frequently vascular brain injury coexisting with Alzheimer-type changes (Schneider et al., 2007; Toledo et al., 2013; Sachdev et al., 2025).

Recent population-based autopsy studies confirm that vascular lesions—particularly small-vessel disease and microinfarcts—lower the threshold at which Alzheimer pathology becomes clinically manifest. Even modest vascular injury can unmask or accelerate cognitive decline in individuals with subclinical amyloid and tau pathology (Alzheimer's Association Workgroup, 2024).

**2 Mechanistic Links Between Vascular Injury and Alzheimer Pathology**
Several mechanisms have been proposed to explain the synergistic interaction between vascular and Alzheimer pathology:

**1. Reduced cognitive reserve:** Vascular injury decreases network redundancy, making the brain more vulnerable to neurodegenerative pathology.
**2. Impaired clearance of amyloid-β:** Small-vessel disease and blood–brain barrier dysfunction reduce perivascular drainage and glymphatic clearance of amyloid (Hainsworth et al., 2024).
**3. Chronic hypoperfusion:** Sustained cerebral hypoperfusion promotes amyloidogenic processing and tau phosphorylation (De la Torre, 2012; updated mechanistic reviews in 2024).
**4. Neuroinflammation:** Vascular injury induces inflammatory cascades that may accelerate neurodegeneration (Mok et al., 2024).

**3 Neuroimaging Evidence of Mixed Pathology**
Modern imaging demonstrates frequent overlap between vascular lesions and Alzheimer biomarkers. WMH and microbleeds are commonly observed in patients with amyloid-positive positron emission tomography (PET) scans, and their presence predicts more rapid cognitive decline than either pathology alone (Charidimou et al., 2022; Alzheimer's Association Workgroup, 2024).

Amyloid PET and cerebrospinal fluid biomarkers have reshaped diagnostic thinking, emphasizing that biological Alzheimer disease and VCID are not mutually exclusive but often coexist within the same individual (Sachdev et al., 2025).

**Table 9. Vascular–Alzheimer Interaction: Key Concepts**

| Aspect | Vascular contribution | Alzheimer contribution |
|---|---|---|
| Cognitive threshold | Lowers reserve | Progressive neurodegeneration |
| Imaging markers | WMH, lacunes, microbleeds | Amyloid/tau PET, hippocampal atrophy |
| Clinical phenotype | Executive dysfunction, gait | Amnestic syndrome |
| Outcome | Faster decline when combined | Greater severity |

**4 Implications for Diagnosis and Classification**
The recognition of mixed pathology has major implications for diagnosis. Contemporary frameworks recommend describing both vascular and Alzheimer contributions, rather than forcing a single etiologic label. This approach improves prognostic accuracy and aligns with biomarker-driven definitions of Alzheimer disease introduced in the early 2020s (Alzheimer's Association Workgroup, 2024; Sachdev et al., 2025).

In geriatric practice, this translates into diagnosing "dementia due to mixed vascular and Alzheimer pathology"when evidence supports both processes, rather than defaulting to a single category.

## Clinical and Research Implications

Understanding the interaction between cerebrovascular injury and Alzheimer pathology reframes vascular dementia from a competing diagnosis to a core modifier of late-life cognitive decline. This perspective has shifted prevention strategies toward aggressive vascular risk factor management across the lifespan and highlights the potential for vascular interventions to delay or attenuate dementia onset, even in biologically defined Alzheimer disease (Mok et al., 2024; Sachdev et al., 2025).

## Clinical Implications and Prevention Strategies

**1 Vascular Risk Factors as Modifiable Drivers of Cognitive Decline**
A central implication of contemporary VaD/VCID research is that vascular risk factors are modifiable contributors to dementia risk across the lifespan. Hypertension, diabetes mellitus, dyslipidemia, smoking, obesity, physical inactivity, and atrial fibrillation are consistently associated with cerebrovascular injury and cognitive decline (Livingston et al., 2024; Mok et al., 2024). Control of these factors reduces stroke incidence and is increasingly recognized as a strategy to delay or prevent dementia onset.

Recent population-based analyses reinforce that midlife vascular risk exposure is particularly detrimental, accelerating later-life cognitive decline and increasing vulnerability to mixed dementia (Livingston et al., 2024). Importantly, risk factor modification remains beneficial even in late life, particularly for reducing progression of small vessel disease and preventing recurrent stroke (Markus, 2023).

**2 Blood Pressure Control and Cerebral Small Vessel Disease**
Hypertension is the most important modifiable risk factor for cerebral small vessel disease. Longitudinal imaging studies from 2022–2024 demonstrate that intensive blood pressure control slows progression of white matter hyperintensities and reduces incident cognitive impairment, particularly executive dysfunction (Hainsworth et al., 2024; Mok et al., 2024).

However, aggressive blood pressure lowering must be individualized in older adults to avoid cerebral hypoperfusion, orthostatic hypotension, and falls. Current geriatric-focused reviews emphasize balancing vascular protection with functional safety, particularly in frail individuals (Sachdev et al., 2025).

**3 Stroke Prevention and Secondary Prevention**
In patients with established cerebrovascular disease, secondary stroke prevention is a cornerstone of VaD management. Antiplatelet therapy, anticoagulation for atrial fibrillation, lipid-lowering therapy, and lifestyle modification reduce recurrent vascular events and may stabilize cognitive trajectories (Ng & colleagues, 2025).

Recent observational data suggest that effective secondary prevention is associated with slower cognitive decline in post-stroke populations, particularly when recurrent infarction is prevented (Chen et al., 2025). These findings underscore the importance of integrating stroke and dementia care pathways.

**4 Implications of Mixed Pathology for Prevention**
Recognition of mixed vascular–Alzheimer pathology reframes prevention strategies. Even in individuals with biomarker-defined Alzheimer disease, vascular risk factor control appears to delay clinical expression and slow functional decline (Alzheimer's Association Workgroup, 2024; Livingston et al., 2024). This reinforces the concept that vascular health is a universal target for dementia prevention, regardless of underlying neurodegenerative pathology.

## Diagnostic Challenges and Differential Diagnosis

**1 Clinical Overlap With Alzheimer's Disease**

Differentiating VaD from Alzheimer's disease remains challenging due to overlapping symptoms and frequent coexistence of pathologies. While VaD typically presents with executive dysfunction, slowed processing speed, and attentional deficits, memory impairment is often present, particularly in mixed dementia (Mok et al., 2024; Sachdev et al., 2025).

Abrupt onset, stepwise decline, focal neurological signs, and prominent gait disturbance favor a vascular contribution, whereas insidious onset and early episodic memory impairment suggest Alzheimer pathology. Nonetheless, reliance on clinical features alone is insufficient, highlighting the importance of neuroimaging and biomarkers.

**2 Role of Neuroimaging in Attribution**

MRI evidence of vascular brain injury is essential for attributing cognitive impairment to vascular causes. However, imaging findings must be interpreted in context. WMH and lacunes are common in aging and may be incidental unless their burden and distribution plausibly explain cognitive deficits (Duering et al., 2023; Ng & colleagues, 2025).

Recent diagnostic frameworks emphasize causal plausibility, requiring that vascular lesions are sufficient in severity and location to account for observed cognitive impairment (Sachdev et al., 2025). This approach reduces overdiagnosis of VaD based solely on imaging abnormalities.

**3 Biomarkers and the Evolving Diagnostic Landscape**

The integration of Alzheimer biomarkers into dementia diagnostics has transformed classification systems. Amyloid and tau biomarkers identify biological Alzheimer disease even in the presence of significant vascular pathology (Alzheimer's Association Workgroup, 2024).

Consequently, many patients previously labeled as VaD are now recognized as having mixed dementia.

This paradigm shift encourages dual attribution and supports tailored management strategies addressing both vascular and neurodegenerative processes.

**Table 10. Diagnostic Considerations in VaD and Mixed Dementia**

| Feature | Suggests Vascular Contribution | Suggests Alzheimer Contribution |
|---|---|---|
| Cognitive profile | Executive dysfunction, slowed processing | Early episodic memory impairment |
| Course | Stepwise or fluctuating | Gradual, progressive |
| Neurological signs | Focal deficits, gait disturbance | Typically absent early |
| MRI findings | WMH, lacunes, infarcts | Medial temporal atrophy |
| Biomarkers | Usually negative | Amyloid/tau positive |

## Disease-Modifying Drugs for Alzheimer's Disease in the Context of Vascular Dementia and VCID

***Overview and core principle***

Disease-modifying drugs (DMDs) for Alzheimer's disease (AD) currently refer primarily to anti-amyloid monoclonal antibodies (mAbs) that reduce brain amyloid-β and modestly slow clinical decline in early symptomatic AD(typically mild cognitive impairment due to AD or mild AD dementia) with biomarker confirmation of amyloid pathology (Cummings et al., 2023; Rabinovici et al., 2025). These therapies are not designed to treat vascular brain injury, and therefore are not indicated for "pure" vascular dementia (VaD) where cognitive impairment is attributable predominantly to infarcts, small-vessel disease, hemorrhagic lesions, or hypoperfusion (Ng et al., 2025).

In clinical reality, many older adults present with mixed pathology (vascular brain injury plus biological AD). In these cases, DMDs may be considered only if the patient meets AD-therapy eligibility (clinical stage and amyloid biomarker positivity) and does not have vascular imaging features that substantially raise hemorrhagic risk (Rabinovici et al., 2025; Cogswell et al., 2024).

***Why DMDs generally do not apply to pure VaD***

Anti-amyloid mAbs target amyloid plaques and associated downstream processes; they do not reverse infarction, repair white matter disconnection from small-vessel disease, or address the hemodynamic/inflammatory mechanisms of vascular cognitive impairment (Ng et al., 2025). Accordingly, the evidence base and appropriate-use recommendations restrict treatment to AD-spectrum phenotypes with amyloid confirmation, not dementia caused predominantly by cerebrovascular disease (Cummings et al., 2023; Rabinovici et al., 2025).

***The practical "mixed dementia" pathway***

For a patient labeled clinically as "vascular dementia," the key question becomes whether there is coexisting AD biology sufficient to justify AD-directed DMDs. The practical pathway is:

1. Establish clinical stage consistent with early AD treatment populations (mild cognitive impairment or mild dementia due to AD) (Cummings et al., 2023; Rabinovici et al., 2025).
2. Confirm amyloid positivity (amyloid PET or CSF biomarkers) (Cummings et al., 2023; Rabinovici et al., 2025).
3. Evaluate MRI for hemorrhagic markers and vascular lesion burden that increase risk and/or indicate that vascular disease is the major driver (Cogswell et al., 2024; Rabinovici et al., 2025).
4. Counsel on realistic benefit (modest slowing), monitoring burden (serial MRI), and the risk profile, especially ARIA (amyloid-related imaging abnormalities) (Cummings et al., 2023; Cogswell et al., 2024).

ARIA and why vascular pathology matters

The dominant safety issue with anti-amyloid mAbs is ARIA, which includes:

- **ARIA-E** (vasogenic edema/effusion)
- **ARIA-H** (microhemorrhages and superficial siderosis)

ARIA risk is influenced by baseline MRI findings consistent with cerebral amyloid angiopathy (CAA) (e.g., multiple lobar microbleeds, cortical superficial siderosis) and by APOE ε4 genotype; importantly, vascular brain disease markers can complicate risk assessment and management (Cummings et al., 2023; Cogswell et al., 2024). Specialized vascular neurology guidance emphasizes the need to integrate cerebrovascular risk factors, antithrombotic use, and hemorrhage-prone imaging features when considering anti-amyloid therapy (Greenberg et al., 2025).

***Baseline MRI exclusions and "vascular-heavy" phenotypes***

Appropriate-use recommendations commonly exclude patients with MRI patterns suggesting high hemorrhagic risk (notably multiple microbleeds or superficial siderosis) and those with a major vascular contribution to cognitive impairment, because the benefit-risk balance becomes unfavorable when vascular injury is the primary driver or when hemorrhagic complications are more likely (Rabinovici et al., 2025). For example, donanemab appropriate-use guidance explicitly notes exclusion in settings such as >4 microbleeds, cortical superficial siderosis, or major vascular contribution to cognitive impairment (Rabinovici et al., 2025). Lecanemab appropriate-use recommendations similarly stress MRI screening, ARIA monitoring schedules, and careful avoidance of high-risk scenarios (Cummings et al., 2023).

***Antithrombotics, stroke history, and clinical safety constraints***

A major real-world issue is concomitant antithrombotic therapy. Many patients with vascular dementia or VCID are receiving antiplatelets or anticoagulation for secondary stroke prevention or atrial fibrillation. Appropriate-use recommendations advise heightened caution and often avoidance with anticoagulants due to hemorrhage risk and ARIA-H concerns (Cummings et al., 2023; Kane, 2024). Vascular neurology guidance further addresses thrombolysis/anticoagulation considerations and emphasizes structured ARIA monitoring and management pathways (Greenberg et al., 2025).

**Table 11. When to consider AD DMDs in a patient with vascular dementia/VCID phenotype**

| Scenario | DMD use rationale | Practical recommendation |
|---|---|---|
| Pure VaD (amyloid negative; vascular injury sufficient to explain dementia) | No AD target | Do not use AD DMDs; focus on vascular prevention and rehabilitation (Ng et al., 2025) |
| Suspected mixed dementia (vascular + AD), amyloid positive, early clinical stage | Potential benefit for AD component | Consider if MRI risk profile acceptable and monitoring feasible (Cummings et al., 2023; Rabinovici et al., 2025) |
| VCID with extensive microbleeds/siderosis or strong CAA pattern | High ARIA/ICH risk | Generally avoid; unfavourable benefit-risk (Cogswell et al., 2024; Rabinovici et al., 2025) |
| VCID requiring anticoagulation (e.g., AF stroke prevention) | Increased hemorrhagic risk | Usually avoid or treat only under strict specialist protocols (Cummings et al., 2023; Kane, 2024; Greenberg et al., 2025) |

**Table 12. Minimum clinical and imaging prerequisites before initiating anti-amyloid therapy (applied to "vascular dementia" referrals)**

| Domain | Minimum requirement | Why it matters |
|---|---|---|
| Clinical stage | Mild cognitive impairment or mild dementia due to AD | Trial-tested population (Cummings et al., 2023; Rabinovici et al., 2025) |
| Biomarkers | Amyloid confirmed by PET or CSF | Confirms target engagement relevance (Cummings et al., 2023) |
| Baseline MRI | Recent MRI with FLAIR + GRE/SWI sequences | ARIA risk stratification (Cogswell et al., 2024; Cummings et al., 2023) |
| Hemorrhagic markers | Absence of high-risk microbleed/siderosis patterns | Reduce ARIA-H/ICH risk (Rabinovici et al., 2025) |
| Medication review | Evaluate antithrombotics, especially anticoagulants | Hemorrhage risk and management complexity (Kane, 2024; Greenberg et al., 2025) |
| Monitoring capacity | Ability to complete scheduled MRIs | ARIA detection and safe continuation (Cummings et al., 2023; Cogswell et al., 2024) |

***Counseling and expectations***

Even when eligible, patients and families should be counseled that anti-amyloid DMDs generally produce modest slowing of decline rather than symptomatic improvement, and that treatment requires frequent visits, infusion capacity, and MRI surveillance—factors that may limit feasibility in frail, multimorbid older adults (Cummings et al., 2023; Jeremic et al., 2025). When vascular disease is prominent, prevention of further vascular injury often delivers clearer benefit (stroke prevention, blood pressure control, rehabilitation) than pursuing an AD-specific DMD with substantial monitoring burden and hemorrhagic risk (Ng et al., 2025).

***Practical recommendation statement for your review***

In patients with dementia attributed to vascular causes, Alzheimer disease–modifying therapy should be considered only when (1) there is biomarker evidence of AD, (2) the patient is in an early symptomatic stage consistent with clinical trial populations, and (3) MRI does not demonstrate a hemorrhage-prone profile or a major vascular contribution that would shift the benefit-risk balance against treatment (Cummings et al., 2023; Rabinovici et al., 2025; Greenberg et al., 2025).

## Synthesis: Reconceptualizing Vascular Dementia

Contemporary evidence supports reconceptualizing vascular dementia not as a discrete disease entity but as a major pathway to cognitive impairment that frequently intersects with neurodegeneration. Cerebrovascular injury disrupts neural networks, lowers cognitive reserve, and accelerates the clinical expression of Alzheimer pathology. This interaction explains the high prevalence of mixed dementia in older populations and underscores the need for integrated diagnostic and management approaches (Sachdev et al., 2025; Livingston et al., 2024).

From a clinical perspective, this synthesis emphasizes prevention, early detection of vascular injury, and aggressive management of vascular risk factors as essential components of dementia care. From a research perspective, it highlights the importance of harmonized imaging standards, domain-based cognitive assessment, and biomarker-informed classification.

## Conclusion

Vascular dementia encompasses a heterogeneous group of cognitive disorders arising from diverse cerebrovascular injuries, including large-vessel infarction, small vessel disease, strategic lesions, hypoperfusion, and hemorrhagic injury. Advances in neuroimaging and neuropathology have clarified how these lesions disrupt cognitive networks and interact with Alzheimer pathology to produce late-life dementia. Modern frameworks emphasize vascular cognitive impairment as a continuum, recognize mixed pathology as the dominant phenotype, and prioritize vascular health as a modifiable determinant of cognitive aging. Continued integration of imaging, biomarkers, and clinical assessment will be critical for improving diagnosis, prevention, and patient-centered care.

## References

Alzheimer's Association Workgroup. (2024). Biological definition of Alzheimer disease: 2024 update and implications for mixed dementia. Alzheimer's & Dementia, 20(3), 345–362.
Bentvelzen, A. C., Aalten, P., de Laat, K. F., van Norden, A. G. W., & de Leeuw, F. E. (2025). Harmonizing cognitive assessment in vascular cognitive impairment: Toward domain-based diagnostic standards. Journal of Alzheimer's Disease, 95(1), 1–14.
Bowler, J. V., Munoz, D. G., Merskey, H., & Hachinski, V. (1997). Factors affecting the age of onset and rate of progression of Alzheimer's disease. Journal of Neurology, Neurosurgery & Psychiatry, 62(5), 531–536.
Cogswell, P. M., Wardlaw, J. M., & Charidimou, A. (2024). Amyloid-related imaging abnormalities: Pathophysiology, risk stratification, and clinical management. Lancet Neurology, 23(5), 421–434.
Cummings, J., Aisen, P., Apostolova, L. G., Atri, A., Salloway, S., & Weiner, M. (2023). Lecanemab: Appropriate use recommendations. Journal of Prevention of Alzheimer's Disease, 10(3), 362–377.
Charidimou, A., Boulouis, G., Gurol, M. E., Ayata, C., Bacskai, B. J., Frosch, M. P., & Greenberg, S. M. (2022). Emerging concepts in sporadic cerebral amyloid angiopathy. Brain, 145(10), 3277–3294.
Chen, Y., Duering, M., Jouvent, E., Reyes, S., De Guio, F., & Chabriat, H. (2025). Network disruption as a mechanism of cognitive impairment in vascular dementia. Neurology, 104(4), e381–e392.
De la Torre, J. C. (2012). Cardiovascular risk factors promote brain hypoperfusion leading to cognitive decline and dementia. Cardiovascular Psychiatry and Neurology, 2012, 367516.
Duering, M., Biessels, G. J., Wardlaw, J. M., Smith, E. E., Zwanenburg, J. J. M., & Jouvent, E. (2023). Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurology, 22(4), 331–345.
Ghika-Schmid, F., & Bogousslavsky, J. (2000). The acute behavioral syndrome of anterior thalamic infarction: A prospective study of 12 cases. Annals of Neurology, 48(2), 220–227.
Gorelick, P. B., Scuteri, A., Black, S. E., Decarli, C., Greenberg, S. M., Iadecola, C., Launer, L. J., Laurent, S., Lopez, O. L., Nyenhuis, D., Petersen, R. C., Schneider, J. A., Tzourio, C., Arnett, D. K., Bennett, D. A., Chui, H. C., Higashida, R. T., Lindquist, R., Nilsson, P. M., … American Heart Association Stroke Council. (2011). Vascular contributions to cognitive impairment and dementia. Stroke, 42(9), 2672–2713.
Greenberg, S. M., Vernooij, M. W., Cordonnier, C., Viswanathan, A., Al-Shahi Salman, R., Warach, S., Launer, L. J., Van Buchem, M. A., & Breteler, M. M. (2009). Cerebral microbleeds: A guide to detection and interpretation. Lancet Neurology, 8(2), 165–174.
Hachinski, V. C., Lassen, N. A., & Marshall, J. (1974). Multi-infarct dementia: A cause of mental deterioration in the elderly. Lancet, 2(7874), 207–210.
Hainsworth, A. H., Minett, T., Andoh, J., Forster, G., Bhide, I., Barrick, T. R., & Markus, H. S. (2024). Neuropathology of cerebral small vessel disease and its contribution to dementia. Acta Neuropathologica, 147(1), 1–24.

Kane, J. P. (2024). Antithrombotic therapy and hemorrhagic risk in patients receiving anti-amyloid monoclonal antibodies. Neurology: Clinical Practice, 14(1), 12–19.
Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., Brayne, C., Burns, A., Cohen-Mansfield, J., Cooper, C., Costafreda, S. G., Dias, A., Fox, N., Gitlin, L. N., Howard, R., Kales, H. C., Kivimäki, M., Larson, E. B., Ogunniyi, A., … Mukadam, N. (2024). Dementia prevention, intervention, and care: 2024 report of the Lancet Commission. Lancet, 403(10431), 139–210.
Markus, H. S. (2023). Cerebral small vessel disease: Pathogenesis and clinical implications. Journal of Neurology, Neurosurgery & Psychiatry, 94(1), 12–21.
Mok, V. C. T., Lam, B. Y. K., Wong, A., Ko, H., Markus, H. S., & Wong, L. K. S. (2024). Early-onset and late-onset vascular dementia: Revisiting clinical phenotypes. Lancet Neurology, 23(2), 180–192.
Ng, A. Y. Y., Black, S. E., & Sachdev, P. S. (2025). Vascular cognitive impairment and dementia: Advances in diagnosis and clinical care. Nature Reviews Neurology, 21(3), 145–162.
O'Brien, J. T., & Thomas, A. (2015). Vascular dementia. Lancet, 386(10004), 1698–1706.
Pantoni, L. (2010). Cerebral small vessel disease: From pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurology, 9(7), 689–701.
Prins, N. D., & Scheltens, P. (2015). White matter hyperintensities, cognitive impairment and dementia. Nature Reviews Neurology, 11(3), 157–165.
Rabinovici, G. D., Gatsonis, C., Apgar, C., et al. (2025). Donanemab appropriate use recommendations and implications for mixed dementia. Alzheimer's & Dementia, 21(2), 201–216.
Roman, G. C., Tatemichi, T. K., Erkinjuntti, T., Cummings, J. L., Masdeu, J. C., Garcia, J. H., Amaducci, L., Orgogozo, J. M., Brun, A., Hofman, A., et al. (1993). Vascular dementia: Diagnostic criteria for research studies. Neurology, 43(2), 250–260.
Sachdev, P. S., Blacker, D., Blazer, D. G., Ganguli, M., Jeste, D. V., Paulsen, J. S., & Petersen, R. C. (2014). Classifying neurocognitive disorders: The DSM-5 approach. Nature Reviews Neurology, 10(11), 634–642.
Sachdev, P. S., Lo, J. W., Crawford, J. D., Mellon, L., Hickey, A., Williams, D., & Leyden, J. (2025). Diagnostic criteria for vascular cognitive impairment: Updated consensus recommendations. Alzheimer's & Dementia, 21(1), 23–41.
Schneider, J. A., Arvanitakis, Z., Leurgans, S. E., & Bennett, D. A. (2007). The neuropathology of probable Alzheimer disease and vascular dementia. Annals of Neurology, 62(4), 337–346.
Silva, A. R., Zsoldos, E., Filippini, N., Mahmood, A., Allan, C. L., Sexton, C. E., Topiwala, A., & Ebmeier, K. P. (2025). Total cerebral small vessel disease burden and cognitive decline in aging. Brain, 148(2), 456–469.
Toledo, J. B., Arnold, S. E., Raible, K., Brettschneider, J., Xie, S. X., Grossman, M., Monsell, S. E., Kukull, W. A., Trojanowski, J. Q., & Shaw, L. M. (2013). Contribution of cerebrovascular disease in autopsy-confirmed neurodegenerative disease cases. Brain, 136(9), 2697–2706.
Wardlaw, J. M., Smith, C., & Dichgans, M. (2019). Small vessel disease: Mechanisms and clinical implications. Lancet Neurology, 18(7), 684–696.

# Letrozole vs clomiphene citrate in the management of infertility in women with polycystic ovary syndrome

**Sahar Mustafa Abobaker Omer** [1], **Malaz Al Zubair Mohamed Khalil** [2]

(1) Family medicine specialist, PHCC, Doha, Qatar
(2) Family medicine specialist, PHCC, Doha, Qatar

**Correspondence**
Dr. Sahar Mustafa Abobaker Omer
Family medicine specialist
PHCC, Doha, Qatar
**Email:** saomer@phcc.gov.qa

Received: November 2025. Accepted: December 2025; Published: January/February 2026.
Citation: Sahar Mustafa Abobaker Omer, Malaz Al Zubair Mohamed Khalil. Letrozole vs clomiphene citrate in the management of infertility in women with polycystic ovary syndrome. World Family Medicine. January/February 2026; 24(1): 39 - 41
DOI: 10.5742/MEWFM.2026.2401023

## Abstract

Background: Poly cystic ovary syndrome (PCOS) is the most common endocrine disorder leading to anovulatory infertility. Both clomiphene citrate and letrozole are widely used for ovulation induction, but their relative effectiveness remains a subject of debate.

In this literature review we critically analyze randomized controlled trials comparing letrozole to clomiphene citrate in respect to:

- main outcome: ovulation rate, pregnancy rate and pregnancy outcome
- secondary outcome: miscarriage rate, endometrial thickness, multiple pregnancy and side effects of the medications

Methodology: A review of published articles was conducted including systematic review and meta-analysis, double blind randomized controlled trails focusing on data from the last 5 years, with the focus of the study on ovulation rate, pregnancy rate and outcome (live birth rates), with some secondary outcomes such as miscarriage rate and endometrial thickness.

Results: Letrozole showed better outcome than clomiphene citrate in terms of mean endometrial thickness, ovulation rate and pregnancy rate and outcomes with better side effect profile observed in some trials.

Key words:
Polycystic ovary syndrome (PCOS), letrozole, clomiphene citrate

## Introduction

The polycystic ovary syndrome (PCOS) is an important cause of both menstrual irregularity and androgen excess in women. PCOS can be readily diagnosed when women present with the classic features of hirsutism, irregular menstrual cycles, and polycystic ovarian morphology on transvaginal ultrasound (TVUS). However, there has been considerable controversy about specific diagnostic criteria when not all of these classic features are evident.

Estimated prevalence of PCOS varies from 6.3% using 2023 International guideline adolescent diagnostic criteria to 9.8% using original Rotterdam PCOS diagnostic criteria in female persons aged 10-19 years (systematic review). The syndrome is characterized clinically by oligomenorrhea and hyperandrogenism, as well as the frequent presence of associated risk factors for cardiovascular disease, including obesity, glucose intolerance, dyslipidemia, fatty liver and obstructive sleep apnea.

The etiology of PCOS is unclear, although it is thought to emerge from a combination of genetic and epigenetic factors, hypothalamic and ovarian dysfunction, excess exposure to androgen, insulin resistance and mechanisms related to excess adiposity.

PCOS is frequently diagnosed in women presenting with infertility issues.

The main management options are:
- management of patient who is not seeking infertility (includes acne, hirsutism, female pattern hair loss and management of menstrual irregularities)
- management of patients who seek fertility (which includes lifestyle modifications and medications)

Letrozole is an aromatase inhibitor and can be used as an oral ovulation induction agent; aromatase inhibitors prevent estrogen biosynthesis from androgens by inhibiting aromatase conversion of androgens to estrogens, including in the ovary.

The decline in estrogen levels leads to an increase in follicle-stimulating hormone through hypothalamic/pituitary feedback, resulting in stimulation of ovarian follicle development and maturation.

Clomiphene citrate is a selective estrogen receptor modulator (SERM) that blocks estradiol receptors in the hypothalamus and induces changes in gonadotropin releasing hormone pulse frequency, leading to release of follicle-stimulating hormone from the anterior pituitary and stimulation of follicular development.

While clomiphene citrate has traditionally been used as first-line therapy for management of anovulatory infertility, letrozole may now be preferred due to the following advantages:

- letrozole preserves ovarian/pituitary feedback (in contrast to clomiphene citrate), which reportedly reduces the risk of multiple follicle development compared to clomiphene citrate
- letrozole does not affect endometrial estrogen receptors (in contrast to clomiphene citrate), and therefore, does not adversely impact endometrial thickness or cervical mucus
- half-life is 2 days for letrozole compared to 5 days for clomiphene citrate

Many studies recommend the use of letrozole as first line for infertility in patients with PCOS with recommendations from: American College of Obstetricians and Gynecologists (ACOG) recommends letrozole as first-line ovulation induction therapy over clomiphene citrate due to increased live birth rate with letrozole compared with clomiphene citrate (ACOG Level A); Use letrozole as the preferred first-line treatment to induce ovulation in patients with anovulatory infertility and no other fertility factors (International PCOS Network Strong recommendation for the option, High-quality evidence).

## Methodology

The literature sources used were PubMed, Cochrane, and Google Scholar. We choose literature published within the last 5 years, namely from 2019-2024. After that, a selection of journals with open access criteria was carried out and literature that met the criteria was obtained in 10 journals.

Studies included were RCTs of infertile women with PCOS (Rotterdam 2003 criteria) comparing clomiphene citrate and letrozole.

Interventions involved timed intercourse or intrauterine insemination.

At least one primary or secondary outcome had to be reported.

Excluded studies were non-clinical, observational, reviews, or animal/cell studies, or involved drug resistance or other infertility causes.

Articles with incomplete data, mixed interventions, irrelevant outcomes, or not in English were also excluded.

Main outcomes: ovulation rate per cycle, clinical pregnancy rate, and live-birth rate.

Secondary outcomes: miscarriage rate per patient and per pregnancy, multiple pregnancy rate per patient and per pregnancy.

Endometrial thickness at midcycle measured by ultrasound was also recorded.

## Results and Discussion

**The Effectiveness of Letrozole Compared to Clomiphene Citrate Based on ovulation rates**

The majority of the included studies reported higher ovulation rates with letrozole when compared to clomiphene citrate.

A systematic review and metanalysis, indicated that letrozole increased the ovulation rate per cycle in patients with PCOS compared with clomiphene citrate (RR 1.14, 95% CI 1.06–1.21, P<.001).

**The Effectiveness of Letrozole Compared to Clomiphene Citrate Based on Pregnancy Rate and outcome**

Overall, available evidence suggests that letrozole may result in higher pregnancy rates and better reproductive outcome (live birth) than clomiphene citrate in patient with PCOS.

Reviewing the latest systematic review letrozole was more effective in promoting pregnancy than clomiphene citrate (34.6% vs 23.4%, RR 1.48, 95% CI 1.34–1.63, P<.001) and higher live births (32.8% vs 22.2%, RR 1.49, 95% CI 1.27–1.74, P<.001).

## Some secondary outcomes

Some studies also highlighted secondary outcomes such as endometrial thickness. It indicated that letrozole was associated with improving endometrial thickness compared with clomiphene citrate (9.02 mm vs 7.55 mm, mean difference 1.50, 95% CI 0.96–2.04, P<.001).

Rates of miscarriage were similar between the two treatment groups; however, treatment with letrozole was associated with fewer multiple pregnancies compared with clomiphene citrate.

At the time of this review, there is a lack of sufficient evidence to fully assess differences in adverse effects between the letrozole group and the clomiphene citrate group.

## Conclusion

Based on this literature review, it was found that Letrozole is superior to Clomiphene Citrate (CC) as an ovulation induction agent in PCOS patients. Letrozole is also associated with a better probability of pregnancy and live birth.

The probability of miscarriage and the occurrence of congenital anomalies or defects in the newborn did not differ between the groups receiving letrozole and those with CC.

## References

-Pundir J, Achilli C, Bhide P, Sabatini L, Legro RS, Rombauts L, et al. Risk of foetal harm with letrozole use in fertility treatment: a systematic review and meta-analysis. Hum Reprod Update 2021;27:474–85. doi: 10.1093/humupd/dmaa055

-Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Fertil Steril 2018;110:364–79.doi: 10.1016/j.fertnstert.2018.05.004

https://journals.lww.com/greenjournal/fulltext/2023/03000/Letrozole_Compared_With_Clomiphene_Citrate_for.11.aspx

-Weiss NS, Kostova E, Nahuis M, Mol BWJ, van der Veen F, van Wely M. Gonadotrophins for ovulation induction in women with polycystic ovary syndrome. Cochrane Database Syst Rev. 2019;1(1):CD010290.

-Franik S, Le QK, Kremer JA, Kiesel L, Farquhar C. Aromatase inhibitors (letrozole) for ovulation induction in infertile women with polycystic ovary syndrome. Cochrane Database Syst Rev. 2022;9(9):CD010287.

-Abu-Zaid A, Gari A, Sabban H, Alshahrani MS, Khadawardi K, Badghish E, et al. Comparison of Letrozole and Clomiphene Citrate in Pregnancy Outcomes in Patients with Polycystic Ovary Syndrome: A Systematic Review and Meta-analysis. Reprod Sci. 2024;31(4):883-905.

-https://www.dynamedex.com/management/management-of-infertility-associated-with-polycystic-ovary-syndrome-pcos#GUID-87017ED2-CC7B-4448-8126-57D876DB6BA3

-https://www.dynamedex.com/management/management-of-infertility-associated-with-polycystic-ovary-syndrome-pcos#GUID-E15F590C-A0FE-4614-9B48-FD098CEA8065

-Bansal, S., Goyal, M., Sharma, C., & Shekhar, S. (2021). Letrozole versus clomiphene citrate for ovulation induction in anovulatory women with polycystic ovarian syndrome: A randomized controlled trial. International Journal of Gynecology and

-Joham, A. E., & Peña, A. S. (2022). Polycystic Ovary Syndromein Adolescence. Seminars in Reproductive Medicine, 40(12). https://doi.org/10.1055/s-0042-1757138

-Fauser BC, Tarlatzis BC, Rebar RW, Legro RS, Balen AH, Lobo R, et al. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Fertil Steril.2012;97(1):28-38.

-https://www.dynamedex.com/condition/polycystic-ovary-syndrome-pcos

-https://www.dynamedex.com/management/management-of-polycystic-ovary-syndrome-pcos

# Glutathione Under Scrutiny: infusion risks?

**Ebtisam Elghblawi**

Correspondence:
Dr Ebtisam Elghblawi
Dermatologist
ORCID: https://orcid.org/0000-0001-7008-3946
**Email**: ebtisamya@yahoo.com

Received: November 2025. Accepted: December 2025; Published: January/February 2026.
Citation: Elghblawi E. Glutathione Under Scrutiny: infusion risks?. World Family Medicine. January/February 2026; 24(1): 42 - 46
DOI: 10.5742/MEWFM.2026.2401024

## Abstract

Skin lightening has long been influenced by socio-cultural perceptions that favour lighter skin tones, leading to widespread use of depigmenting agents. Across the years, many have been used, such as mercury, hydroquinone, and potent steroids. Glutathione, a naturally occurring tripeptide with potent antioxidant and anti-melanogenic properties, has gained popularity for its skin-whitening effects. It modulates melanogenesis by inhibiting tyrosinase activity, shifting melanin production from eumelanin to pheomelanin, and reducing oxidative stress induced by ultraviolet radiation. Glutathione is available in oral, topical, and parenteral forms. Evidence suggests that oral and topical formulations, particularly when combined or enhanced with micro-needling, are relatively safe and may improve skin tone and texture. However, intravenous glutathione remains controversial due to limited clinical evidence, lack of standardised dosing, transient effects, and reports of serious adverse events, including renal failure and severe cutaneous reactions. Despite this, unregulated promotion and self-medication persist. Robust, large-scale clinical trials are urgently needed to establish efficacy, safety, and ethical considerations before recommending glutathione, particularly intravenous formulations, for cosmetic skin lightening.

This paper will critically review the biological basis, clinical evidence, safety, and ethical implications of glutathione use for skin lightening, with particular emphasis on comparing oral, topical, and intravenous routes, highlighting the risks of unregulated cosmetic use, and guiding dermatologists toward evidence-based and safe practice.

Keywords: glutathione, skin lightening, intravenous, infusion, parenteral.

## Introduction

There is considerable activity surrounding the use of glutathione in conjunction with vitamins, as well as other additives such as vitamin C, collagen, and various micronutrients, administered parenterally in the context of skin lightening, detoxification, and anti-aging. The promotion of it has occurred due to the strong commercial marketing as a magical wonder for whitening skin by certain pharmaceutical companies, on social media platforms. In Libya, it took a toll, and in many places worldwide, the dream of whiteness is a mystical thing. Furthermore, it is not licensed and not regulated by the Food and Drug Administration (FDA) or European Medicines Agency (EMA)(1-3).

Additionally, in certain nations and ethnicities, it is promoted as a wellbeing injection for detoxing and whitening and taken systemically, as an intravenous drip, and is widely offered in the UK by the aesthetic clinics, and in some countries, like the Philippines it's taken far more than any other nation, besides India, Pakistan, Singapore, Thailand, Malaysia, China, and Indonesia. I came across some of my Filipino patients taking it intravenously, with no evidence and is unlicensed for that use and it is administered by non-medically qualified beauticians, without consistent regulation. Further glutathione has some recent warning of serious side effects, such as anaphylaxis, kidney and liver problems which mandate a call for action by the decision makers and the relevant authorities.

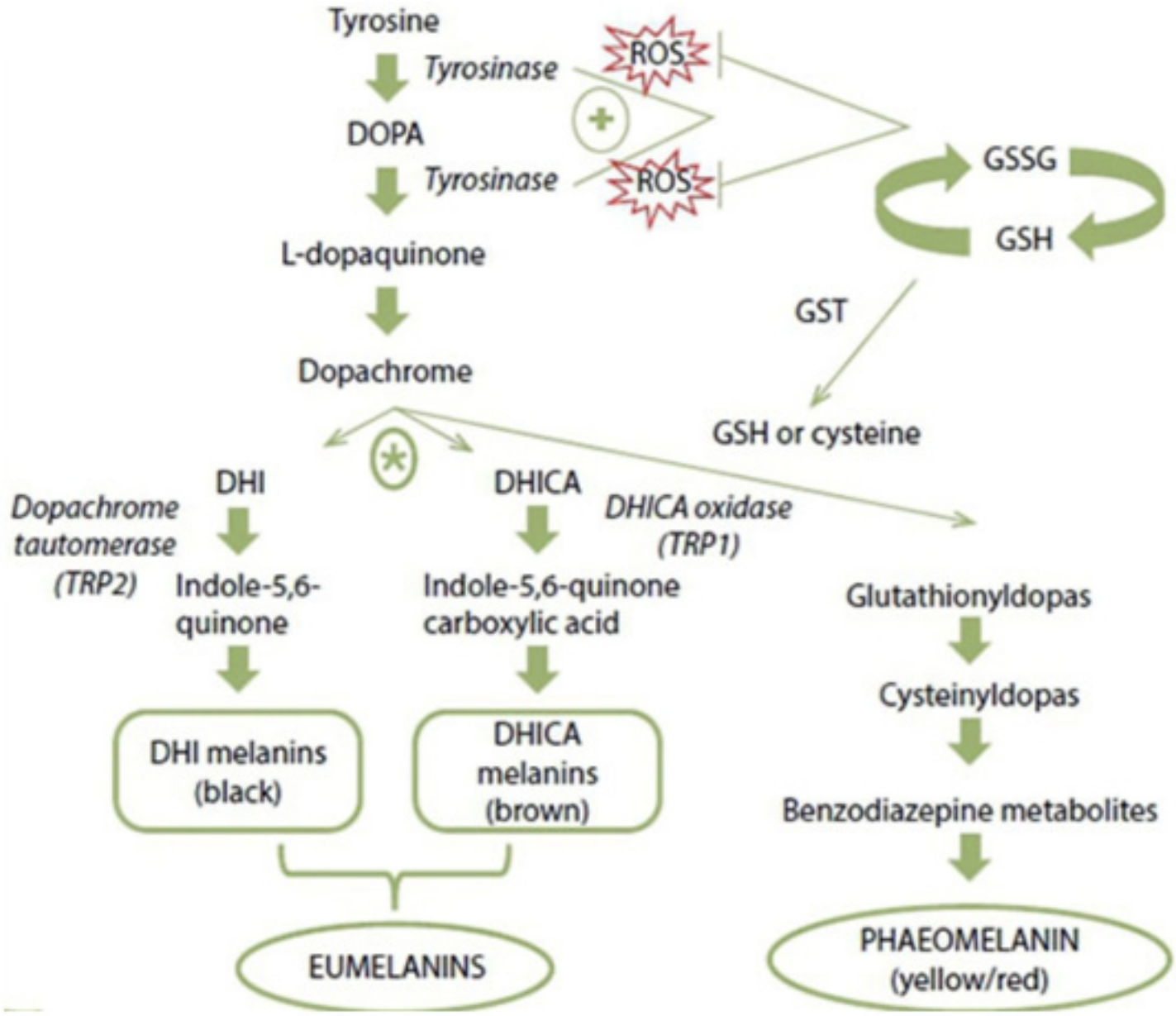
There has been preoccupation and obsession with whiteness in certain nations and in those with darker skin. The general tale is that a fairer complexion is beautiful, preferable, and alluring. Thus, many women and some men would revert to skin whitening, and thus marketing companies exploit that obsession. Across the years, many depigmentary therapies have been devised and utilised in different skin conditions, including for melasma and post inflammatory pigmentation (1).

## Glutathione structure

Glutathione is a small, low-molecular-weight, water-soluble molecule. It's a tripeptide molecule composed of amino acids L-cysteine, glycine, and glutamate, which is synthesized intracellularly(6).

Glutathione is one of the most used antioxidant agents in humans (protects against ultraviolet induced damage and improves skin elasticity) that has anti-melanogenic properties and has gained widespread popularity. Also it shifts the process of melanogenesis from the darker eumelanin to the lighter molecules of phaeomelanin. It lessens melanin production and thus reduces hyperpigmentation, and reduces oxidation of tyrosinase, which is the crucial factor in melanin production, and modulates melanin production (Figure 1). Glutathione exists in two forms, the reduced (GSH) and the oxidized form (GSSG), in a balanced ratio GSH: GSSG, and the former is linked to the depigmentatory functionality, as it is intracellular with potent antioxidative properties (defends against toxic particles and prevents oxidative damage needed for cell survival), and is constantly oxidised to GSSG by the glutathione peroxidase enzyme. Any imbalance as a marker for oxidative stress, is reported in many diseases such as cancer, neurodegenerative disorders, cystic fibrosis, diabetes, anorexia, low birth weight neonates, and autism (6). Additionally, it plays a role in the body's defence system, scavenges free radicals, and reduces oxidative stress.

**Figure 1: melanogenesis, David et al, 2016.**



## Human skin colour

Human skin colour is determined by the amount of melanin, which is synthesised from tyrosine, through the melanogenesis. The ratio of melanin found in skin, black-brown eumelanin and yellow-red pheomelanin, determines the skin colour, where lighter skin colour implies increased pheomelanin (Figure 1). This might lead to UV skin photosensitivity and DNA damage. GSH has the potential to lighten human skin, which is lower in black human skin than in white skin (6).

Ultraviolet exposure and heat cause hyperpigmentation, where tyrosinase activity increases, resulting in excessive amounts of reactive oxygen and nitrogen within cells (1).

The lightening effects of glutathione were an accidental discovery as a side effect of a larger dose of it, as it directly inhibits tyrosinase by chelating the copper site with the thiol group, and at the cellular level, transferring tyrosinase to premelanosomes, and by antioxidant effects indirectly inhibiting tyrosinase.

Glutathione scavenges the ultraviolet radiation-induced reactive oxygen generated in epidermal cells (2).

## Medical conditions and glutathione

There are certain medical conditions where glutathione is depleted, such as emphysema, asthma, allergic disorders, drug toxicity, metabolic disorders, cancer, chemotherapy with cisplatin, human immunodeficiency virus, and acquired immune deficiency syndrome.

## Glutathione forms and routes

Glutathione is administered in three forms, oral, topical, and parenteral, as a skin whitening agent. The generalised method was twice weekly for at least eight to ten weeks to notice the changes. The oral and the topical glutathione have shown some appealing positive results in terms of lightening and improving texture of the skin, especially if both were combined, and proven to be safe and effective as well as well tolerated, without any concerns. Additionally, microneedling shows enhanced effects of the topical glutathione as it enhances its penetration through the micro-tunnelling of the skin. Whereas the intravenous route is considered concerning and controversial and short-lived, as it fades after six months, besides the concerning side effects and no standardised dosing protocols.

## Glutathione: Miracle or Myth?

Most of the studies were small samples conducted on healthy volunteers for a short period of time, with poor study design, no long-term follow-up, no serum level glutathione measurement, and some of the participants had experienced skin lightening.

Despite a lack of clinical evidence for their effectiveness and lasting skin whitening tone, manufacturers, distributors, spas, and clinics kept promoting and recommending them. Some had experienced various liver dysfunction and disorders, and had no pre-tests done to assess the progress and changes. Others reported risks are renal failures, severe fatal skin reactions like toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), systemic inflammatory response syndrome (SIRS), skin cancer which might be due to depletion and switch from brown melanin to red which increases sun induced skin cancer, skin aging, immune system suppression, severe abdominal pain, thyroid dysfunction, air embolism, and blood sepsis from untrained staff or use of counterfeit intravenous glutathione (1-3).

Additionally, some of those forms are available over the counter (OTC) and online for purchase. The manufacturer advised that the rapid skin whitening can be achieved by a high dose of 600-1200 mg, twice a week injection, with an undefined duration to keep the desirable changes. Furthermore, those injections are sold expensively. The only indication is to reduce the neurotoxicity associated with cisplatin chemotherapy.

Many patients are inclined to self-medicate with glutathione, lured by the manufacturers' claims and the aesthetician and the spa promotion (3).

## Natural glutathione

Glutathione can be found in fresh fruits, vegetables, and nuts. Also, tomatoes, avocados, oranges, walnuts, and asparagus are other sources to increase the level of glutathione inside our body (3).

## Discussion and Conclusion

Oral and topical forms are safe for cosmetic and therapeutic uses within specific guidelines and are well tolerated with minor side effects. Most reported assessments were done based on photography (6). Whilst skin brightening and lighter tones might improve individual socioeconomic status and opportunities, it risks reinforcing structural racism (3).

Unregulated IV glutathione products are considered debatable as they can cause life-threatening health issues, along with cross-reactions with other drugs, and pose significant risks. Non-prescription cosmetic infusions should be scrutinised. Further rigorous and robust research with clinical evidence is needed on a larger scale to evaluate the efficiency and effectiveness of those cosmetic infusions, to reach long-term safety with an optimised, thoroughly investigated dose before recommending it (4).

Patients should refrain from buying over-the-counter glutathione skin-lightening products, particularly those that may contain or be combined with mercury (6).

It would be sensible for dermatologists to refrain from processing such injections for skin lightening until rigorous further clinical trials and high-quality studies are conducted to establish a safe use of it. Urgent measures are required to protect consumers from potential adverse effects and complications associated with intravenous infusions (6). Additionally, raising awareness about its potential risks, where statutory remains elusive should be mandatory.

Finally, the psychosocial consequences of systemic skin lightening represent a complex and sensitive topic that is best addressed through a multidisciplinary approach involving dermatologists, social scientists, psychologists, and psychiatrists.

## References

1. Sonthalia S, Daulatabad D, Sarkar R. Glutathione as a skin whitening agent: Facts, myths, evidence, and controversies. Indian J Dermatol Venereol Leprol. 2016 May-Jun;82(3):262-72. doi: 10.4103/0378-6323.179088. PMID: 27088927.
2. Alzahrani TF, Alotaibi SM, Alzahrani AA, Alzahrani AF, Alturki LE, Alshammari MM, Alharbi RA, Alanazi SI, Alshammari WZ, Algarni AS. Exploring the Safety and Efficacy of Glutathione Supplementation for Skin Lightening: A Narrative Review. Cureus. 2025 Jan 27;17(1):e78045. doi: 10.7759/cureus.78045. PMID: 40013212; PMCID: PMC11862975.
3. Sharma D, Daram S, Sharma P. Systemic Inflammatory Response Syndrome Following High-Dose Intravenous Glutathione-Containing Revitalising Solution in a Patient on Tirzepatide: A Case Report. Cureus. 2025 May 24;17(5):e84736. doi: 10.7759/cureus.84736. PMID: 40556995; PMCID: PMC12185258.
4. Khanna R, Rambhia P, Chapas A. Systematic Review of the Efficacy and Safety of Topical Glutathione in Dermatology. J Clin Aesthet Dermatol. 2025 Sep;18(9):51-54. PMID: 41416233; PMCID: PMC12710870.
5. Sonthalia S, Jha AK, Lallas A, Jain G, Jakhar D. Glutathione for skin lightening: a regnant myth or evidence-based verity? Dermatol Pract Concept. 2018;8(1):15-21. DOI: https://doi.org/10.5826/dpc.0801a04
6. DAVIDS, L M; VAN WYK, J C and KHUMALO, N P. Intravenous glutathione for skin lightening: Inadequate safety data. SAMJ, S. Afr. med. j. [online]. 2016, vol.106, n.8 [cited 2026-01-23], pp.782-786. Available from: <http://www.scielo.org.za/scielo.php?script=sci_arttext&pid=S0256-95742016000800022&lng=en&nrm=iso>. ISSN 2078-5135. https://doi.org/10.7196/samj.2016.v106i8.10878

# Persistent Primary Spontaneous Pneumothorax in a Young Smoker in Qatar

**Sahar A. Al-Kurbi**

**Correspondence:**
Dr.Sahar Alawi Al-Kurbi, MD
Specialist Family Medicine
PHCC, Doha- Qatar
**Email:** sahar.alkurbi@gmail.com

Received: November 2025. Accepted: December 2025; Published: January/February 2026.
Citation: Sahar A. Al-Kurbi. Persistent Primary Spontaneous Pneumothorax in a Young Smoker in Qatar. World Family Medicine. January/February 2026; 24(1): 47 - 53 DOI: 10.5742/MEWFM.2026.2401025

## Abstract

A 19 year old male patient presented with sharp right-sided chest pain. He was diagnosed with a large right pneumothorax after a chest XR. Early diagnosis led to the prompt transfer of the patient to secondary care, where he received appropriate management. This case illustrates the importance of a detailed history and physical examination, as well as early diagnosis of a serious medical emergency, since a young patient can initially compensate well despite the severe pneumothorax on imaging.

Keywords:
Pneumothorax, primary spontaneous pneumothorax, bulbectomy, chest tube, VATS

## Case presentation

A 19 years old male patient came to the clinic with a sharp, stabbing, right-sided chest pain that started 10 minutes prior to presentation while he was driving. The pain is worse with inspiration. He also had a mild cough that started 2 weeks ago with common cold symptoms. He denied any history of trauma, fever, productive cough, shortness of breath, or radiation of the pain. He is a chronic smoker with a 4-pack-year history. No recent travel history. He expected that this was a musculoskeletal pain, as he took a cold shower in the morning. No past medical or surgical history. No known allergies.

On examination, his vital signs were within normal. Temperature: 37 C, blood pressure: 121/81 mmHg, heart rate: 85, respiratory rate: 20, oxygen saturation: 99%. He was a thin male with BMI of 21. Sitting comfortably on the bed, he was comfortable, speaking full sentences, and wasn't tachypneic. Chest examination was normal without hyper-resonance on percussion; there was bilateral air heard over the lungs, no wheezing or rhonchi. No chest wall tenderness to palpation.

A chest XR was ordered to rule out spontaneous pneumothorax, since the patient was young, thin, and a smoker. Chest XR showed a right-sided large pneumothorax with left-sided shifting of mediastinum elements (Figure 1). EMS were called, and the patient was transferred urgently to Hamad Medical Corporation Emergency Department via ambulance. Upon arrival to the ED, the patient developed shortness of breath and tachypnea (his respiratory rate was 28); his other vital signs remained stable. Chest XR was repeated (Figure 2), which showed worsening of the pneumothorax and a complete right-sided lung collapse. A chest tube was inserted, which resulted in full lung expansion (Figure 3) and improvement in the patient's chest pain and dyspnea.

He was admitted for observation. On the third day, however, a repeated chest x-ray showed a redemonstration of right-sided pneumothorax. Thus, the thoracic surgery team were consulted, and a high-resolution CT scan was ordered (Figure 4). The CT scan showed right apical lung bullae around 20 mm, moderate right pneumothorax, and partial collapse of the right lung. Then the patient underwent VATS bullectomy and pleurectomy. Post-operatively, a chest x-ray showed lung re-expansion. The patient was discharged home with follow-up in the thoracic surgery clinic.

**Figure 1 First chest x-ray showing Large right pneumothorax with left sided shifting of mediastinum elements**

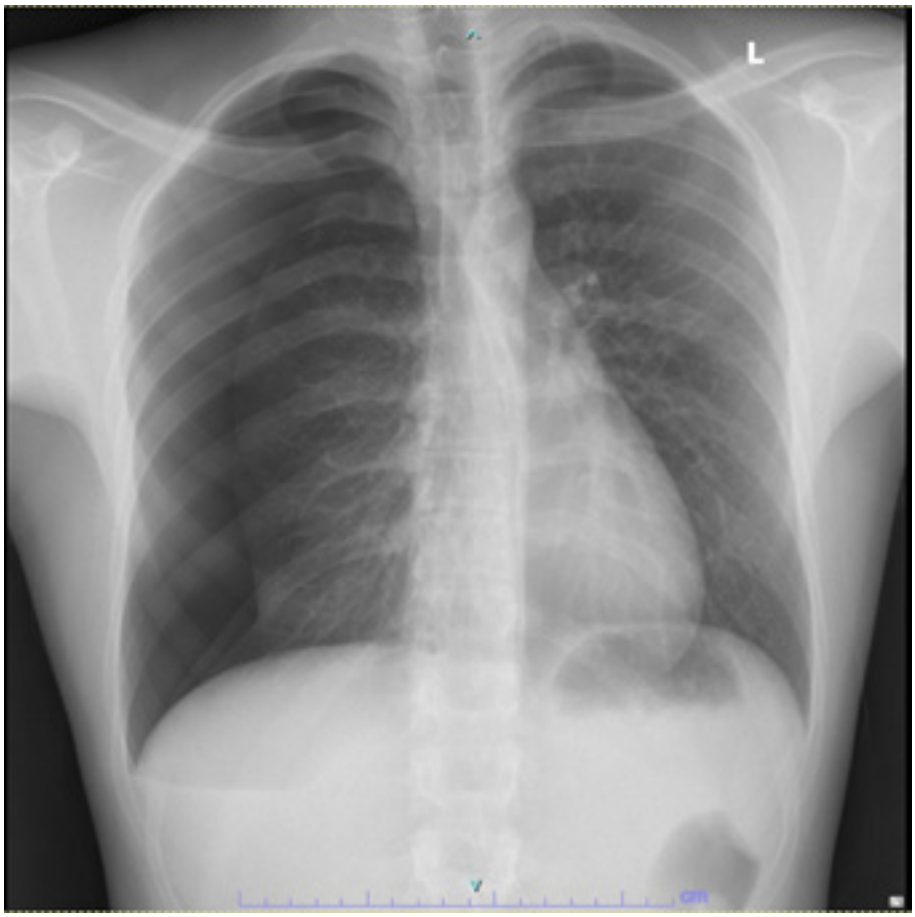



**Figure 2 showing right sided pneumothorax with right lung collapse**

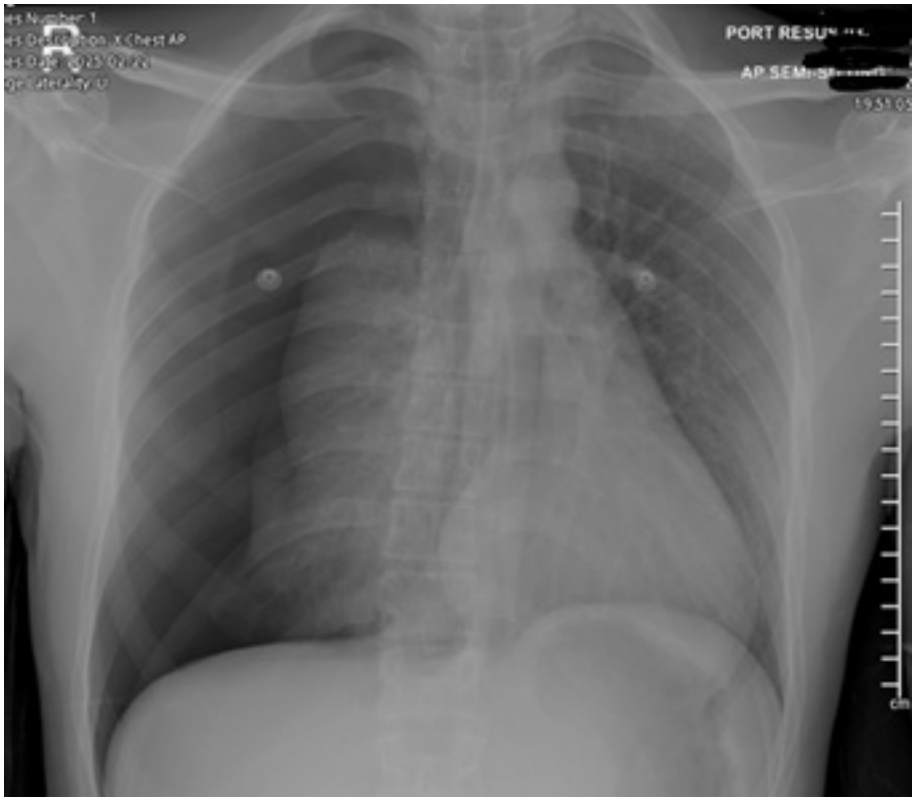


**Figure 3 showing lung re-expansion after chest tube insertion**

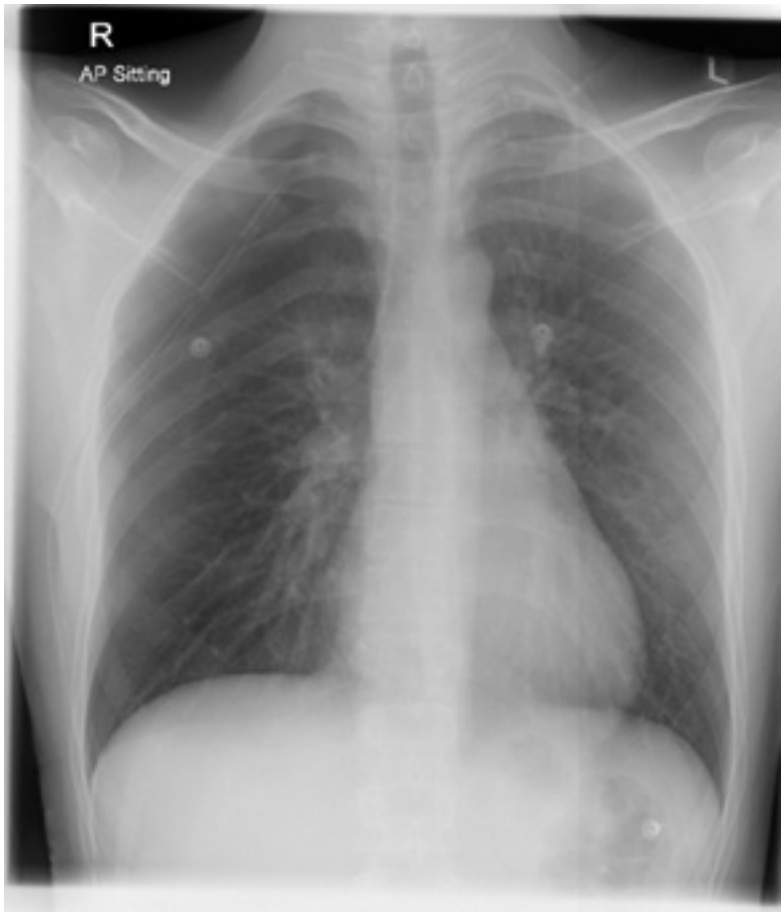
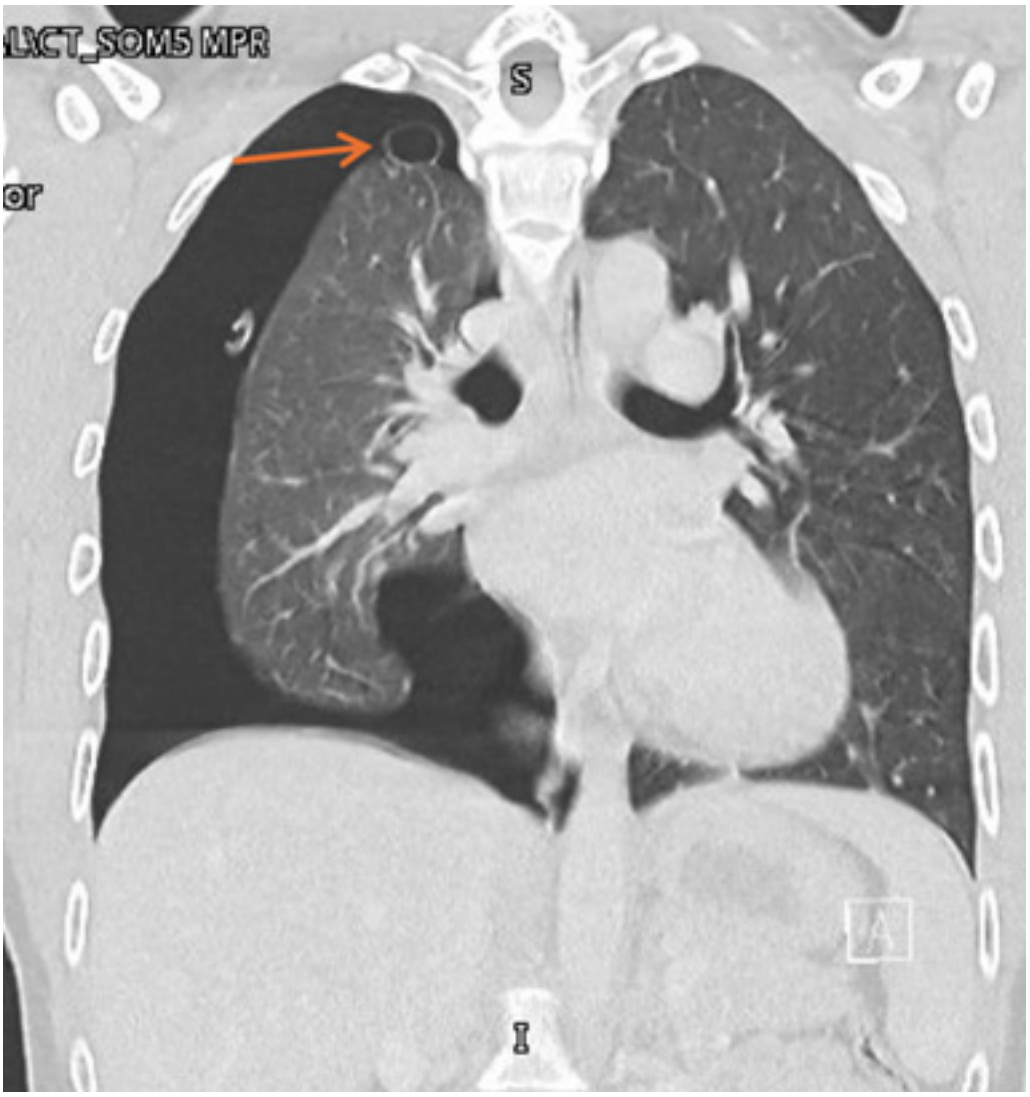


**Figure 4: Coronal CT scan showing right apical lung bullae and right pneumothorax with partial collapse of the right lung**



## Discussion

Spontaneous pneumothorax is defined as air or gas that accumulates in the pleural space without an external precipitating factor [1,2]. Primary spontaneous pneumothorax happens in patients without underlying lung disease [1]. It happens at 20-30 years of age [2]. It is more common in men compared to women, with a ratio of 3:1 [1, 3]. The most important risk factor for developing PSP is smoking [1]. In a study conducted in Sweden, smoking increases the relative risk of the first attack of pneumothorax by a factor of 22 in men and 9 in women. Other risk factors include tall, thin body habitus, pregnancy, Marfan syndrome, and familial pneumothorax [2].

PSP presents as an acute episode of pleuritic chest pain. The differential diagnosis of pleuritic chest pain ranges from life-threatening diseases that need prompt diagnosis and treatment in secondary care to simple illnesses that can be managed with conservative management in primary care. In a primary care setting, the most important task of the physician is to rule out alarming symptoms. In this case, the patient's young age, gender, and smoking history were all risk factors for pneumothorax [4]. On examination, hyper-resonance and diminished breath sounds are noted on the affected side. Diagnosis is clinical but is confirmed by an upright posteroanterior (PA) chest radiograph [1]. The difficulty does not lie in the diagnosis but in having a low threshold for clinical suspicion in a stable patient without an obvious precipitating factor. A patient's condition can shift from stable vitals to respiratory failure very quickly [4].

The recurrence in PSP ranges from 25% to 54%, with underlying chronic lung disease as a significant factor for recurrence [3]. In a Spanish study, PSP recurrence rarely happens 3 years following the first episode. Moreover, smoking cessation decreases the risk of PSP recurrence by a factor of 4 [5]. Thereby, smoking cessation is crucial to prevent recurrence [4]. In addition, it was found to be higher in patients with lung blebs or bullae who were managed conservatively and those who have low haemoglobin and low leukocytes [6].

In a retrospective study done in Qatar, risk factors for developing PSP in the 223 participants were male gender (90.7% of study participants), thin build (mean BMI of 21.7), and smoking history (51.2% of participants). The recurrence rate in the study was 2.66%. It has been mentioned that men dominate the population in Qatar with 74.9% compared to women due to a high number of male expatriates, thereby explaining the high gender difference in the study [7].

Treatment of PSP depends on the clinical presentation. It can range from conservative management to surgical intervention. In patients with small asymptomatic primary spontaneous pneumothorax, observation with follow-up in the outpatient setting in 2-4 weeks is appropriate. If patients become symptomatic, they need decompression with either a needle or a chest tube. When patients are unstable, large-needle decompression with a 14—16 gauge needle is used. After the patient becomes stable, a thoracostomy tube is inserted [2]. Some patients need surgical interventions such as VATS or thoracotomy. Indications for surgical interventions are continuous air leak, bilateral pneumothoraces, high-risk profession patients (divers and pilots), recurrent ipsilateral pneumothorax, and patients who have AIDS [2]. Some studies have found that VATs are superior to thoracotomy in terms of a lower rate of recurrence, lower length of hospitalization, faster functional recovery, and cosmetic results [3].

## Conclusions

Pneumothorax, especially when it becomes a tension pneumothorax, is a life-threatening disease. This case illustrates the importance of a detailed history and physical examination, as well as early diagnosis of a serious medical emergency, since a young patient can initially compensate well despite the severe pneumothroax on imaging.

## References

1. Noppen M. Spontaneous pneumothorax: epidemiology, pathophysiology and cause. European Respiratory Review [Internet]. 2010 Aug 31;19(117):217–9. Available from: https://err.ersjournals.com/content/errev/19/117/217.full.pdf
2. McKnight CL, Burns B. Pneumothorax [Internet]. National Library of Medicine. StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441885/
3. Mendogni P, Vannucci J, Ghisalberti M, Anile M, Aramini B, Congedo MT, et al. Epidemiology and management of primary spontaneous pneumothorax: a systematic review. Interactive CardioVascular and Thoracic Surgery [Internet]. 2020 Mar 1;30(3):337–45. Available from: https://academic.oup.com/icvts/article/30/3/337/5681660
4. Segraves JM, Dulohery MM. Primary spontaneous pneumothorax due to high bleb burden. Respiratory Medicine Case Reports. 2016;19:109–11.
5. Hallifax R. Aetiology of Primary Spontaneous Pneumothorax. Journal of Clinical Medicine. 2022 Jan 19;11(3):490.
6. Riveiro-Blanco V, Pou-Álvarez C, Ferreiro L, Toubes ME, Quiroga-Martínez J, Suárez-Antelo J, et al. Recurrence of primary spontaneous pneumothorax: Associated factors. Pulmonology [Internet]. 2022 Jul 1;28(4):276–83. Available from: https://www.sciencedirect.com/science/article/pii/S2531043720301379
7. Ahmad Khan A, Zahid M, Ahmad Alhiyari M, Ahmad Al-Andulmalek A, Ekpuk Jumbo U, Naser Kloub M, et al. Demographics, clinical characteristics, and recurrence rate of patients with primary spontaneous pneumothorax at a tertiary care center in Qatar. Qatar Medical Journal

# The terms normal weight, overweight and obesity should be replaced with the amount of excess fat tissue in the human body

**Mehmet Rami Helvaci[1], Esma Helvaci[2], Emine Helvaci[2], Yusuf Aydin[1], Leyla Yilmaz Aydin[3], Alper Sevinc[1], Celaletdin Camci[1]**

1 Specialist of Internal Medicine, MD, Turkey
2 Manager of Writing and Statistics, Turkey
3 Specialist of Pulmonary Medicine, MD, Turkey

**Correspondence:**
Prof Dr Mehmet Rami Helvaci
07400, ALANYA, Turkey
Phone: 00-90-506-4708759
**Email:** mramihelvaci@hotmail.com

Received: November 2025. Accepted: December 2025; Published: January/February 2026.
Citation: Helvaci M R et al. The terms normal weight, overweight and obesity should be replaced with the amount of excess fat tissue in the human body. World Family Medicine. January/February 2026; 24(1): 54 - 70 DOI: 10.5742/MEWFM.2026.2401026

## Abstract

Background: Excess fat may be the major cause of atherosclerosis, aging, and death.

Methods: Sickle cell diseases (SCD) patients were studied.

Results: We studied 222 males and 212 females (30.8 vs 30.3 years of age, 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), stroke (12.1% vs 7.5%, p<0.05), chronic renal disease (CRD) (9.9% vs 6.1%, p<0.05), cirrhosis (8.1% vs 1.8%, p<0.001), chronic obstructive pulmonary disease (25.2% vs 7.0%, p<0.001), coronary heart disease (18.0% vs 13.2%, p<0.05), leg ulcers (19.8% vs 7.0%, p<0.001), and digital clubbing (14.8% vs 6.6%, p<0.001) were all higher in males.

Conclusion: As an accelerated atherosclerotic process, hardened RBC-induced capillary endothelial damage terminates with end-organ insufficiencies in early decades in the SCD. Although atherosclerotic endpoints are so common, we detected no case of diabetes mellitus (DM) probably due to lower excess fat tissue. As the most common cause of CRD, DM may be a relative insufficiency of pancreas against the excess fat tissue. But the term of excess weight should be replaced with the amount of excess fat tissue in human body since there are approximately 19 kg of excess fat tissue even between the lower and upper borders of normal weight, 33 kg between the lower border of normal weight and obesity, and 66 kg between the lower border of normal weight and morbid obesity in adults.

Key words: Sickle cell diseases, excess fat tissue, endothelial inflammation, atherosclerosis, normal weight, overweight, obesity, acarbose, metformin

## Introduction

Chronic endothelial damage initiated at birth may be the most common cause of aging and death via the atherosclerotic endpoints in human being (1). Much higher blood pressures (BP) of the arterial system may be the strongest accelerating factor by means of the repeated injuries on vascular endothelium. Probably, whole afferent vasculature including capillaries are chiefly involved in the catastrophic process. Therefore venosclerosis is not a significant health problem in medicine. Due to the chronic endothelial damage, inflammation, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic natures, which terminally reduce blood supply to the end-organs, and increase systolic and decrease diastolic BP further. Some of the well-known accelerating factors of the inflammatory process are physical inactivity, emotional stress, animal-rich diet, smoking, alcohol, excess fat tissue, chronic inflammation, prolonged infection, and cancers for the development of atherosclerotic endpoints including overweight, obesity, hypertension (HT), diabetes mellitus (DM), chronic renal disease (CRD), coronary heart disease (CHD), cirrhosis, chronic obstructive pulmonary disease (COPD), peripheric artery disease (PAD), stroke, abdominal angina, osteoporosis, dementia, aging, and death (2, 3). Although early withdrawal of the accelerating factors can delay the atherosclerotic endpoints, the endothelial changes can not be reversed, completely due to fibrotic natures. The accelerating factor and atherosclerotic endpoints have been researched under the titles of metabolic syndrome, aging syndrome, and accelerated endothelial damage syndrome in the literature, extensively (4-6). Similarly, sickle cell diseases (SCD) are highly catastrophic process on vascular endothelium initiating at birth and terminating with an accelerated atherosclerosis-induced end-organ insufficiencies even at childhood (7, 8). Hemoglobin S causes loss of elastic and biconcave disc shaped structures of red blood cells (RBC). Loss of elasticity instead of shape may be the main problem because the sickling is rare in peripheric blood samples of cases with associated thalassemia minors (TM), and survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during whole lifespan, but exaggerated with inflammation, infection, cancer, surgery, and emotional stress. The hardened RBC-induced chronic endothelial damage, inflammation, and fibrosis terminate with tissue hypoxia in whole body (9). As a difference from other causes of chronic endothelial damage, SCD keep vascular endothelium particularly at the capillary level since the capillary system is the main distributor of the hardened RBC into the body (10, 11). The hardened RBC-induced chronic endothelial damage causes an accelerated atherosclerosis in much earlier decades. Vascular narrowing and occlusions-induced tissue ischemia, infarct, and end-organ failures are the final endpoints, so the life expectancy is decreased 35 years or more in the SCD because we have patients with the age of 96 years without the SCD but just with the age of 59 years with the SCD.

## Material and Methods

The study was performed in the Medical Faculty of the Mustafa Kemal University between March 2007 and June 2016. All patients with the SCD were included. SCD are diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Smoking, alcohol, acute painful crises per year, transfused units of RBC in their lifespans, leg ulcers, stroke, surgeries, deep venous thrombosis (DVT), epilepsy, and priapism were researched in all patients. Patients with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers. A physical examination was performed by the Same Internist, and patients with disseminated teeth losses (<20 teeth present) were detected. Patients with acute painful crisis or any other inflammatory or infectious process 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 magnetic resonance imagings (MRI) of brain and hips were performed. Other bones for avascular necrosis were scanned according to the patients' complaints. Avascular necrosis of bones is diagnosed via MRI (12). Associated TM were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC since SCD with associated TM come with milder clinics than the sickle cell anemia (SCA) (Hb SS) alone (13). Systolic BP of the pulmonary artery of 40 mmHg or greater are accepted as pulmonary hypertension (14). Cirrhosis is diagnosed with full physical examination, laboratory parameters, and ultrasonographic evaluation of the liver. 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, dyspnea, and 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 is diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity. CRD is diagnosed with a permanently elevated serum creatinine level of 1.3 mg/dL or higher in males and 1.2 mg/dL or higher in females. 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 taken in case of an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is performed in case of a positive exercise electrocardiogram. As a result, CHD

was diagnosed either angiographically or with the Doppler echocardiographic findings as movement disorders in the heart walls. Rheumatic heart disease is diagnosed with the echocardiographic findings, too. Stroke is diagnosed by the CT and/or MRI of the brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in case of visual complaints. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

## Results

We included 222 males and 212 females with similar mean ages (30.8 vs 30.3 years, $p>0.05$, respectively) into the study, and there was no patient above the age of 59 years. Associated TM were detected with similar prevalences in both genders (72.5% vs 67.9%, $p>0.05$, respectively). Smoking (23.8% vs 6.1%) and alcohol (4.9% vs 0.4%) were both 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%, $p<0.001$), CRD (9.9% vs 6.1%, $p<0.05$), cirrhosis (8.1% vs 1.8%, $p<0.001$), COPD (25.2% vs 7.0%, $p<0.001$), CHD (18.0% vs 13.2%, $p<0.05$), 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. 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, the mean ages of the atherosclerotic endpoints 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)*** |
| ***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)*** |
| ***CRD**** | ***9.9% (22)*** | ***<0.05*** | ***6.1% (13)*** |
| ***Stroke*** | ***12.1% (27)*** | ***<0.05*** | ***7.5% (16)*** |
| PHT*** | 12.6% (28) | Ns | 11.7% (25) |
| Autosplenectomy | 50.4% (112) | Ns | 53.3% (113) |
| DVT**** and/or varices and/or telangiectasias | 9.0% (20) | Ns | 6.6% (14) |
| Rheumatic heart disease | 6.7% (15) | Ns | 5.6% (12) |
| Avascular necrosis of bones | 24.3% (54) | Ns | 25.4% (54) |
| Sickle cell retinopathy | 0.9% (2) | Ns | 0.9% (2) |
| Epilepsy | 2.7% (6) | Ns | 2.3% (5) |
| 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 §Coronary heart disease
¶Chronic obstructive pulmonary disease **Chronic renal disease ***Pulmonary hypertension
****Deep venous thrombosis *****Acute chest syndrome

**Table 3: Mean ages of endpoints 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 major cause of vasculitis, aging, and death, and overweight, obesity, and morbid obesity may be irreversible atherosclerotic endpoints in human body. Excess fat tissue causes both excess external pressure on and internal narrowing of vasculature in addition to the already increased blood and insulin needs of the excess tissue. DM may be an irreversible atherosclerotic endpoint caused by the excess fat tissue in whole body rather than the pancreas alone. Although all kinds of atherosclerotic consequences are so common with the SCD, we detected no case of DM in the present study probably due to the lower excess fat tissue in them. The body mass indexes (BMI) were 20.7 vs 24.9 kg/m2 in the SCD and control groups with the mean age of 28.6 years, respectively (p= 0.000) (10). The body heights were similar in both groups (166.1 vs 168.5 cm, respectively, p>0.05) indicating that the height is determined, genetically (10). Similarly, just 20% of elderly have DM, but 55% of patients with DM are obese. So excess fat tissue may be much more risky than aging, smoking, alcohol, or chronic inflammatory or infectious processes for DM. Excess fat tissue leads to a chronic and low-grade inflammation on vascular endothelium, and risk of death from all causes increases parallel to its severity (19). The low-grade chronic inflammation may also cause genetic changes on the endothelial cells, and the systemic atherosclerotic process may even decrease clearance of malignant cells by the natural killers (20). The chronic inflammatory process is characterized by lipid-induced injury, invasion of macrophages, proliferation of smooth muscle cells, endothelial dysfunction, and increased atherogenicity (21, 22). Excess fat tissue is considered as a strong factor for controlling of C-reactive protein (CRP) because the excess tissue produces biologically active leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines (23, 24). On the other hand, excess fat tissue will also aggravate myocardial hypertrophy and decrease cardiac compliance further. Fasting plasma glucose (FPG), triglycerides, and low density lipoproteins (LDL) increased and high density lipoproteins (HDL) decreased parallel to the increased BMI (25). Similarly, CHD and stroke increased parallel to the increased BMI (26). Finally, the risk of death from all causes increased parallel to the increased excess fat tissue in all age groups, and people with underweight may even have lower biological ages and longer overall survival (27). Similarly, calorie restriction prolongs survival and retards age-related chronic sicknesses (28). So the term of excess weight should be replaced with the amount of excess fat tissue in human body since there are approximately 19 kg of excess fat tissue even between the lower and upper borders of normal weight, 33 kg between the lower borders of normal weight and obesity, and 66 kg between the lower borders of normal weight and morbid obesity (BMI ≥ 40 kg/m2) in adults. Interestingly, overweight and obesity are usually started to develop in early childhood. Actually, excess fat tissue may not be an indicator of overeating instead it may just show relative physical and mental inactivity. In another definition, excess fat tissue may be a problem of movement instead of eating. People with hyperactivity even in the normal ranges of body weight may eat much higher than people with overweight or obesity. It is well known that the physical and mental activities increase insulin sensitivity, and prevent development of DM, HT, and other atherosclerotic consequences. But the physical and mental activities should be regular and continuous. Actually, they should be the routine habits of life such as walking even in mild and moderate distances, not using elevator, not using dishwasher, preparing meal at home, plant nutrition, self cleaning of home or workplaces, getting a family and children, spending time with the family members, getting a regular job, trying to do some repairs by themselves, avoiding of retirement as much as possible, getting some daily, weekly, monthly, yearly, and decadely purposes to live for an endless life, asking questions about what I did today and what will I do tomorrow just before sleeping, etc. In another definition, people must be engaged into the life with several logical aims. On the other hand, the overweight, obesity, and morbid obesity may be irreversible illnesses since getting weight decreases physical activities a bit further, and decreased physical activities bring excess fat tissue further. Therefore the fighting with excess fat tissue should be started even in childhood, and the main targets should be the increased mental and physical activities instead of the decreased eating alone. In another definition, people can eat how much they can burn.

DM is the most common cause of blindness, non-traumatic amputation, and hemodialysis in adults. As the most common cause of CRD, DM may be an irreversible atherosclerotic consequence affecting the pancreas, too. Increased blood and insulin needs of the excess fat tissue in contrast to the decreased blood supply of the excess tissue and pancreas both due to excess external pressure on and internal narrowing of the vasculature may be the underlying mechanisms of DM. For instance, excess fat tissue in the liver and pancreas are called as non-alcoholic fatty liver disease (NAFLD) and non-alcoholic fatty pancreas disease (NAFPD). They are usually accepted as the components of the metabolic syndrome. NAFLD progresses to steatohepatitis, cirrhosis, and hepatocellular carcinoma. Blocking triglycerides secretion, subcellular lipid sequestration, lipolysis deficiency, enhanced lipogenesis, gluconeogenesis defects, or inhibition of fatty acid oxidation may be some of the development mechanisms (29). NAFLD may just be an atherosclerotic process, and strongly associated with an accelerated atherosclerotic process not only in the liver instead in whole body. For example, NAFLD is seen in one-third of cases with hepatitis B virus-related chronic liver disease (30). Similarly, higher fatty liver ratios were observed in children with non-Hodgkin lymphomas (31). The liver density on contrast abdominopelvic CT of colorectal cancer patients was low that is consistent with the NAFLD (32). As one of the APR, serum thrombopoietin levels increased in the NAFLD (33). Although serum

levels of oxidizing agents including nitrate and advanced oxidation protein products increased, serum nitrite did not adequately increase as an antioxidant agent in the NAFLD (34). As a result, NAFLD is associated with an impaired carotid intima-media thickness (IMT) and flow-mediated dilation which are considered as early markers of systemic atherosclerosis (35). Carotid IMT was correlated with the BMI ($p<0.001$), age ($p= 0.001$), and grade 2-3 NAFLD ($p<0.001$) (36). Patients with the NAFLD have more complex CHD, and carotid IMT and grade 2-3 NAFLD were associated with the severity of CHD ($p<0.001$ for both) (36-38). Similarly, there were reductions in hepatic artery flow volume, portal vein flow volume, and total flow volume in contrast to the increased NAFLD (39). As the most common pathology of pancreas in adults, there may be reductions in flow volume of pancreatic arteries in the NAFPD, too (40). NAFPD is usually associated with the aging, increased BMI, and insulin resistance (41). Replacement of more than 25% of pancreas by fat tissue is associated with the risks of systemic atherosclerosis and DM (42). Insulin is stored in vacuoles in beta cells of islets of Langerhans in whole pancreas and released via exocytosis. Pancreatic fat infiltration may lead to a reduced insulin secretion (43). NAFPD may lead to exocrine pancreatic insufficiency by fat droplet accumulation in pancreatic acinar cells and consequent lipotoxicity, destruction of acinar cells by both inflammation and fatty replacement, and by negative paracrine effect of adipocytes (44). It is unsurprising that the NAFPD may even cause pancreatic fibrosis and cancers. NAFPD causes a higher risk of DM (42), and newly diagnosed patients with DM have higher pancreatic fat (45). DM may actually be a relative insufficiency of the pancreas against the excess fat tissue in whole body. Age-related impairment of beta cells may actually be an atherosclerotic endpoint since 20% of elderly have DM, and just 55% of patients with DM are obese. Glucose tolerance progressively decreases by aging. It may be due to the progressively decreased physical and mental activity-induced excess fat tissue secreting adipokines. There is no term of malnutrition-related DM. DM can be cured by gastric bypass surgery in 90% of morbid obesity (46). The effect is not due to the weight loss instead decreased insulin requirement daily because it usually occurs just after days of the surgery. This surgery reduced death rate from all causes by 40% (46). NAFPD is an independent risk factor for CHD, too (47). Similarly, NAFPD is associated with increased aortic IMT and epicardial fat tissue (48). Parallel to the NAFLD terminating with cirrhosis, NAFPD may terminate with DM as an atherosclerotic endpoint (49).

Smoking may be the second most common cause of vasculitis all over the body. It causes a systemic inflammation on vascular endothelium terminating with atherosclerotic endpoints (50). Its atherosclerotic effects are the most obvious in the Buerger's disease and COPD (51). Buerger's disease is an obliterative vasculitis in the small and medium-sized arteries and veins, and it has never been reported in the absence of smoking in the literature. Its characteristic features are chemical toxicity, inflammation, fibrosis, and narrowing and occlusions of arteries and veins. Claudication is the most significant symptom with a severe pain in feet and hands caused by insufficient blood supply during exercise. It may also radiate to central areas in advanced cases. Numbness or tingling of the limbs is also a common symptom in them. Skin ulcerations and gangrene of fingers or toes are the terminal endpoints. 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 the main cause of severity of Buerger's disease in the lower extremities. Several narrowing and occlusions of the arm and legs are diagnostic in the angiogram. Skin biopsies may be risky, because a poorly perfused area will not heal, completely. Although most patients are heavy smokers, the limited smoking history of some patients may support the hypothesis that Buerger's disease may be an autoimmune reaction triggered by some constituents of tobacco. Although the only treatment way is complete cessation of smoking, the already developed narrowing and occlusions are irreversible. Due to the well-known role of inflammation, anti-inflammatory dose of aspirin in addition to the low-dose warfarin may even be life threatening by preventing microvascular infarctions. On the other hand, FPG and HDL may be negative whereas triglycerides, LDL, erythrocyte sedimentation rate, and CRP positive acute phase reactants (APR) in smokers (52). Similarly, smoking was associated with the lower BMI due to the systemic inflammatory effects (53, 54). An increased heart rate was detected just after smoking even at rest (55). Nicotine supplied by patch after smoking cessation decreased caloric intake in a dose-related manner (56). Nicotine may lengthen intermeal time, and decrease amount of meal eaten (57). 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 (58). Although the CHD was detected with similar prevalences in both genders, prevalences of smoking and COPD were higher in males against the higher white coat hypertension, BMI, LDL, triglycerides, HT, and DM in females (59). The risk of myocardial infarction is increased three-fold in men and six-fold in women with smoking (60). Chemical toxicity of smoking can affect all organ systems. For instance, it is usually associated with irritable bowel syndrome (IBS), chronic gastritis, hemorrhoids, urolithiasis, and depression with many possible mechanisms (61). First of all, smoking may also have some anxiolytic properties. Secondly, smoking-induced vascular inflammation may disturb epithelial absorption and excretion in the gastrointestinal (GI) and genitourinary (GU) tracts (62). Thirdly, diarrheal losses-induced urinary changes may cause urolithiasis (63). Fourthly, smoking-induced sympathetic nervous system activation may cause motility problems in the GI and GU tracts terminating with IBS and urolithiasis. Finally, immunosuppression secondary to smoking may terminate with the GI and GU tract infections and urolithiasis because some types of bacteria can provoke urinary supersaturation, and modify the environment to

form crystal deposits. Actually, 10% of urinary stones are struvite stones which are built by magnesium ammonium phosphate produced by urease producing bacteria. As a result, urolithiasis was higher with IBS (17.9% vs 11.6%, p<0.01) (61).

CHD is the other major cause of death in the human being together with the stroke. The most common triggering cause is the disruption of an atherosclerotic plaque in an epicardial coronary artery, which leads to a clotting cascade. The plaques are the gradual and unstable collection of lipids, fibrous tissue, and white blood cells (WBC), particularly the macrophages in arterial walls in decades of life. 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 takes its place which may also cause life threatening arrhythmias because the scar tissue conducts electrical impulses more slowly. The difference in conduction velocity between the injured and uninjured tissues can trigger re-entry or a feedback loop that is believed to be the cause of 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. Ventricular tachycardia may also cause sudden cardiac death that usually results in rapid heart rates preventing effective cardiac pumping. Cardiac output and BP may fall to dangerous levels which can lead to further coronary ischemia and extension of the infarct. This scar tissue may even cause ventricular aneurysm and rupture. Aging, physical inactivity, animal-rich diet, excess fat tissue, smoking, alcohol, emotional stress, prolonged infection, chronic inflammation, and cancers are important in atherosclerotic plaque formation. Moderate physical exercise is associated with a 50% reduced incidence of CHD (64). Probably, excess fat tissue may be the most important cause of CHD since there is a high percentage of adults with heavier fat tissue masses than their lean body masses that brings a greater stress not only on the heart but on the liver, kidneys, lungs, brain, and pancreas.

Acute painful crises are nearly pathognomonic for the SCD. Although some authors reported that pain itself may not be life threatening directly, infection, medical or surgical emergency, or emotional stresses are the most common precipitating factors of the crises (65). The increased basal metabolic rate during such stresses aggravates the sickling and capillary endothelial damage, inflammation, and edema terminating with hypoxia and infarcts in whole body. So the risk of mortality is much higher during such crises. Actually, each crisis may complicate with the following crises by leaving sequelaes on the capillary system. After a period of time, the sequelaes may terminate with end-organ failures and sudden death even with a silent crisis. Similarly, after a 22-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 (66, 67). Rapid RBC supports are usually life-saving, although preparation of RBC units usually takes a period of time. Beside that RBC supports in emergencies become much more difficult in terminal cases due to the repeated transfusions and interestingly aging-induced blood group mismatch. Actually, transfusion of each unit complicates the following transfusions via the blood subgroup mismacth. Due to the efficacy of hydroxyurea, RBC transfusions should be preserved just for acute stress and emergencies (66-68). According to our experiences, simple and repeated transfusions are superior to exchange (69, 70). First of all, preparation of one or two units of RBC suspensions in each time provides time to clinicians by preventing sudden death. Secondly, transfusions of one or two units in each time decrease the severity of pain, and relax the patients and their relatives since RBC transfusions probably have the strongest analgesic effects (71). Actually, the decreased severity of pain by transfusions also indicates the decreased severity of inflammation in whole body. Thirdly, transfusions of lesser units will decrease transfusion-related complications including infections, iron overload, and blood group mismatch. Fourthly, transfusions in the secondary health centers prevent deaths developed during the transport to the tertiary centers for the exchange. Terminally, cost of the simple transfusions on insurance system is much lower than the exchange which 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. Probably, leukocytosis contributes to the pathogenesis by releasing cytotoxic enzymes. The adverse effects of WBC on vascular endothelium are of particular interest for atherosclerotic endpoints. For example, leukocytosis even in the absence of any infection was an independent predictor of the severity of the SCD (72), and it was associated with the risk of stroke (73). Disseminated tissue hypoxia, releasing of inflammatory mediators, bone infarctions, and activation of afferent nerves may take role in the pathophysiology of the intolerable pain. Due to the severity of pain, narcotic analgesics are usually required (74), but simple transfusions are effective both to relieve pain and to prevent sudden deaths which may develop due to the end-organ failures on atherosclerotic background of the SCD.

Hydroxyurea is the life-saving drug for the SCD (75). It interferes with the cell division by blocking the formation of deoxyribonucleotides via the 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 (76, 77). 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 catastrophic process is probably exaggerated by the patients' own WBC and PLT. So suppression of proliferation of them can limit the endothelial damage-induced edema, ischemia, and infarctions (78). Similarly, 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 need of RBC transfusion. The outcomes were so overwhelming in the favour of hydroxyurea group 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, annually (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, annually ($p<0.000$) with an additional decreased severity of them (7.8/10 vs 2.2/10, $p<0.000$) (66). Similarly, adults using hydroxyurea for frequent painful crises appear to have reduced mortality rate after a 9-year follow-up period (81). Although the genetic severity remains as the main factor to determine prognosis, hydroxyurea may decrease severity of disease and prolong survival (81). The complications start to be seen even after birth. For example, infants with lower hemoglobin levels were more likely to have higher incidences of ACS, painful crises, and lower neuropsychological scores, and hydroxyurea reduced the incidences of all (82). If started early, hydroxyurea may protect splenic function, improve growth, and delay atherosclerotic endpoints. But due to the risks of infections, iron overload, and development of allo-antibodies causing subsequent transfusions much more difficult, RBC transfusions should be preserved for acute stress and emergencies.

Aspirin is a member of nonsteroidal anti-inflammatory drugs (NSAID). Although aspirin has similar anti-inflammatory effects with the other NSAID, it also suppresses the normal functions of PLT, irreversibly. 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 the synthesis of prostaglandins (PG) and thromboxanes (TX). 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. TX are responsible for the aggregation of PLT to form blood clots. Low-dose aspirin 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 anymore. But aspirin has no effect on the blood viscosity. The antithrombotic property is useful to reduce the risks of myocardial infarction, transient ischemic attack, and stroke (83). Low-dose of aspirin is effective to prevent the second myocardial infarction, too (84). 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 should not be prescribed for febrile patients under the age of 16 years (86), 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, annually (88). Symptoms of Reye syndrome may include personality changes, confusion, seizures, and loss of consciousness (87). Although the liver toxicity and enlargement typically occurs in most cases, jaundice is usually not seen (87). Although the death occurs in 20-40% of cases, about one third of survivors get a significant degree of brain damage (87). It usually starts just after recovery from a viral infection, such as influenza or chicken pox. About 90% of children are associated with an aspirin use (88, 89). Inborn errors of metabolism are the other risk factors, and the genetic testing for inborn errors of metabolism became available in developed countries in the 1980s (87). When aspirin was withdrawn for children in the US and UK, a decrease of more than 90% in Reye syndrome was seen in the 1980s (88). Due to the much lower risk of Reye syndrome but much higher risk of death, aspirin must be added into the acute and chronic phase treatments with an anti-inflammatory dose even in childhood in the SCD (90).

Warfarin is an anticoagulant, and it has no effect on blood viscosity, too. It is the best suited for anticoagulation in areas of slowly flowing blood such as veins and the pooled blood behind artificial and natural valves and dysfunctional cardiac atria. It is commonly used to prevent DVT and pulmonary embolism, and against stroke in atrial fibrillation (AF), valvular heart disease, and artificial heart valves. It is additionally used following ST-segment elevation myocardial infarction and orthopedic surgeries. Initiation regimens are simple, safe, and suitable to be used in the ambulatory settings (91). It should be initiated with a 5 mg dose, or 2 to 4 mg in the elderlies. In the protocol of low-dose warfarin, the target international normalised ratio (INR) is between 2.0 and 2.5, whereas in the protocol of standard-dose warfarin, the target INR is between 2.5 and 3.5 (92). Simple discontinuation of the drug for five days is 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. Warfarin decreases blood clotting by blocking vitamin K epoxide reductase, an ezyme that reactivates vitamin K1. Without sufficient active vitamin K1, abilities of clotting factors II, VII, IX, and X are decreased. The abilities of anticlotting protein C and S are also inhibited, but to a lesser degree. A few days are required for full effect which is lasting up to five days. The consensus

agrees that current self-testing and management devices are effective providing outcomes possibly better than achieved, clinically. The risk of severe bleeding is just 1-3%, annually, and the severest ones are those involving the central nervous system (93, 94). 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). Thirteen publications from 11 cohorts including more than 48.500 patients with more than 11.600 warfarin users were included in the meta-analysis in which warfarin resulted with a lower risk of ischemic stroke ($p= 0.004$) and mortality ($p<0.00001$), but had no effect on major bleeding ($p>0.05$) in patients with AF and non-end-stage CRD (96). Warfarin is associated with significant reductions in ischemic stroke even in patients with warfarin-associated intracranial hemorrhage (ICH) (97). On the other hand, patients with cerebral venous thrombosis (CVT) anticoagulated either with warfarin or dabigatran had lower risk of recurrent venous thrombotic events (VTE), and the risks of bleeding were similar in both regimens (98). Additionally, an INR value of 1.5 achieved with an average daily dose of 4.6 mg warfarin, has resulted with no increase in the number of men ever reporting minor bleeding episodes (99). Non-rheumatic AF increases the risk of stroke, and long-term use of low-dose warfarin is highly effective and safe with a reduction of 86% ($p= 0.0022$) (100). The mortality rate was significantly lower in the warfarin group, too ($p= 0.005$) (100). The frequencies of bleedings that required hospitalization or transfusions were similar in both groups ($p>0.05$) (100). Additionally, very-low-dose warfarin was safe and effective for prevention of thromboembolism in metastatic breast cancer in which the average daily dose was 2.6 mg, and the mean INR value 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 bleedings as for warfarin, but increased GI bleeding (102). Interestingly, rivaroxaban and low-dose apixaban were associated with increased risks of all cause mortality compared with warfarin (103). The mortality rates were 4.1%, 3.7%, and 3.6% per year in the warfarin, 110 mg of dabigatran, and 150 mg of dabigatran groups with AF, respectively ($p>0.05$ for both) (104). Eventually, infection, inflammation, medical or surgical emergency, and emotional stress-induced increased basal metabolic rate accelerates sickling, and an exaggerated capillary endothelial edema-induced myocardial infarction or stroke may cause sudden deaths (105). So anti-inflammatory dose of aspirin plus low-dose warfarin may be the other life-saving drug regimens even at childhood in the SCD (106).

COPD is the third leading cause of death at the moment (107). Aging, smoking, alcohol, male gender, excess fat tissue, chronic inflammation, prolonged infection, and cancers may be the 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 second common cause of COPD due to the excess fat tissue-induced atherosclerotic endpoints in whole body since an estimated 25-45% of patients with the COPD have never smoked (108). Regular alcohol consumption may be the third leading cause of the systemic exaggerated atherosclerotic process and COPD, since COPD was one of the most common diagnoses in alcohol dependence (109). Furthermore, 30-day readmission rates were higher in the COPD patients with alcoholism (110). Probably an accelerated atherosclerotic process is the main structural background of functional changes that are characteristics of the COPD. The inflammatory process of vascular endothelial cells is exaggerated by release of various chemicals by inflammatory cells, and it terminates with an advanced fibrosis, atherosclerosis, and pulmonary losses. COPD may just be the pulmonary endpoint of the systemic atherosclerotic process since there are several reports about coexistence of associated endothelial inflammation in whole body in the COPD (111). For example, there may be close relationships between COPD, CHD, PAD, and stroke (112). 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 multicenter study of 5.887 smokers (113). When hospitalizations were researched, the most common causes were the cardiovascular diseases, again (113). In another study, 27% of mortality cases were due to the cardiovascular diseases in the moderate and severe COPD (114). Finally, COPD may be an irreversible atherosclerotic endpoint in the SCD, too (107).

Leg ulcers are seen in 10% to 20% of patients with the SCD, and its prevalence increases with aging, male gender, and SCA (115, 116). The leg ulcers have an intractable nature, and around 97% of them relapse in one year (115). Similar to Buerger's disease, the leg ulcers occur in the distal segments of the body with a lesser collateral blood flow (115). The hardened RBC-induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillaries may be the main causes (116). 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. Smoking and alcohol probably have some additional atherosclerotic effects on the leg ulcers in males. Although presence of a continuous damage of hardened RBC on vascular endothelial cells, severity of the destructive process is probably exaggerated by the immune system. The main action way of hydroxyurea may be the suppression of hyperproliferative WBC and PLT in the SCD (78). Similarly, lower WBC counts were associated with lower crisis 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 suggest that the ulcers may be due to the increased WBC and PLT counts-induced capillary endothelial edema.

Digital clubbing is characterized by the increased normal angle of 165° between the nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (117). The chronic tissue hypoxia is highly suspected in its etiology (118). 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 smoking and pulmonary, cardiac, renal, and hepatic diseases which are characterized with chronic tissue hypoxia (5). As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs those can affect their functions in a short period of time. On the other hand, digital clubbing is also common in the SCD, too and its prevalence is 10.8% in the present study. It probably shows chronic tissue hypoxia caused by disseminated endothelial damage, edema, and fibrosis, particularly at the capillary level in the SCD. Beside the effects of SCD, smoking, alcohol, cirrhosis, CRD, CHD, and COPD, the higher prevalence of clubbing in males (14.8% vs 6.6%, $p<0.001$) may also indicate some additional role of male gender for the atherosclerotic endpoints.

CRD is increasing which can be explained by prolonged survival and increased prevalence of excess fat tissue, too (119). Aging, animal-rich diet, excess fat tissue, smoking, alcohol, chronic inflammatory or infectious process, and cancers may be the major causes of the renal endothelial inflammation, too. The 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 (120). Excess fat tissue-induced hyperglycemia, dyslipidemia, elevated BP, and insulin resistance can cause tissue inflammation and immune cell activation (121). Age ($p= 0.04$), high-sensitivity CRP ($p= 0.01$), mean arterial BP ($p= 0.003$), and DM ($p= 0.02$) had significant correlations with the CIMT (119). 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 (122). 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 (122). However, along with the increased BP, these changes cause chronic endothelial damage in kidneys in long term (123). 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, CRD progresses more easily (122). The systemic inflammatory effects of smoking on endothelial cells is also important in the CRD (124). Although the presence of some opposite reports (124), alcohol probably gives harm to the renal vascular endothelium, too. Chronic inflammatory or infectious processes may terminate with atherosclerotic endpoints in kidneys, too (123). There are close relationships between CRD and other atherosclerotic endpoints (125, 126). The most common causes of death were CHD and stroke in the CRD, again (127). The hardened RBC-induced capillary endothelial damage may be the cause of CRD in the SCD (128).

Stroke is the other terminal cause of death, together with the CHD, and it develops as an acute thromboembolic event on the chronic atherosclerotic background. Aging, male gender, smoking, alcohol, excess fat tissue, chronic inflammatory or infectious process, cancer, and emotional stress may be the major causes. Stroke is also a common atherosclerotic endpoint of the SCD (129). Similar to the leg ulcers, stroke is particularly higher in cases with the SCA and higher WBC counts (130). Sickling-induced capillary endothelial damage, activations of WBC, PLT, and coagulation system, and hemolysis may terminate with chronic capillary endothelial damage, edema, and fibrosis (131). Stroke may not have a macrovascular origin instead a diffuse capillary endothelial edema may be important in the SCD. Thus permanent neurological deficits are rare with stroke in the SCD. Infection, inflammation, medical or surgical emergency, and emotional stress may cause stroke by increasing basal metabolic rate and sickling. Low risk of stroke with hydroxyurea can also suggest that a significant proportion of stroke is developed due to the increased WBC and PLT counts-induced an acute capillary endothelial edema (132).

Acarbose is a pseudotetrasaccharide produced as a natural microbial product of Actinoplanes strain SE 50. It binds to oligosaccharide binding site of alpha-glucosidase in the brush border of the small intestinal mucosa with a dose-dependent manner, reversibly and competitively. It inhibits glycoamylase, sucrase, maltase, dextranase, and pancreatic alpha-amylase. It has little affinity for isomaltase but does not have any effect on beta-glucosidases such as lactase. By this way, it delays the intestinal hydrolysis of oligo- and disaccharides mainly in the upper half of the small intestine. As a result, the absorption of monosaccharides is delayed, and transport into the circulation is interrupted. Its effects may prolong up to 5 hours. The suppression of alpha-glucosidases is persistent with long-term use. Its usage results with carbohydrates appearing in the colon where bacterial fermentation occurs, and causes flatulence, loose stool, and abdominal discomfort (133). If started with a lower dosage and titrated slowly, side effects are tolerable (134). Long-term use increases colonic bacterial mass that of lactobacteria in particular. The finally impaired carbohydrate absorption, increased bacterial carbohydrate fermentation, and fecal acidification mimic effects of lactulose in portosystemic encephalopathy. So acarbose has a favourable therapeutic profile for the long-term use even in cirrhosis. Similarly, observed changes in bacterial flora and decreased stool pH and beta-

hydroxybutyrate may be associated with anti-proliferative effects on the epithelial cells of colon that may potentially decrease carcinogenesis. Less than 2% of the unchanged drug enters into the circulation. Thus there is no need for dosage adjustment in mild renal insufficiency. After a high carbohydrate meal, acarbose lowers the postprandial rise in blood glucose by 20% and secondarily FPG by 15% (135). The initial improvement in blood glucose tends to be modest, but efficacy steadily improves. It also affects serum lipids with a dose-dependent manner, because dietary carbohydrates are key precursors of lipogenesis (135). Carbohydrate-induced postprandial triglycerides synthesis is reduced for several hours, so acarbose lowers triglycerides (135). The same effect is also seen in non-diabetic patients with hypertriglyceridemia, and acarbose reduced LDL, and HDL remained as unchanged in hyperinsulinemic and overweight patients with impaired glucose tolerance (IGT) (136). Elevated ursocholic acids in the stool appear to be the additive endpoint of a decreased rate of absorption and increased intestinal motility due to the changes of intestinal flora. Acarbose may lower LDL via increased fecal bifido bacteria and biliary acids. Acarbose together with insulin was identified to be associated with a greater improvement in the oxidative stress and inflammation (137). Probably, acarbose improves release of glucagon-like peptide-1, inhibits PLT activation, increases epithelial nitrous oxide synthase activity and nitrous oxide concentrations, promotes weight loss, decreases BP, and eventually prevents endothelial dysfunction (135). So it prevents atherosclerotic endpoints of excess fat tissue even in the absence of IGT or DM (138, 139). Although some authors reported as opposite (140), it should be used as the first-line antidiabetic agent. Based on more than 40 years of use, numerous studies did not show any significant side effect (141). Although 25.9% of patients stopped metformin due to excessive anorexia (142), only 10.6% stopped acarbose due to excessive flatulence or loose stool (143).

Metformin is a biguanide, and it is not metabolized, and 90% of absorbed drug is eliminated as unchanged in the urine. Plasma protein binding is negligible, so the drug is dialyzable. According to literature, antihyperglycemic effect of metformin is largely caused by inhibition of hepatic gluconeogenesis, increased insulin-mediated glucose disposal, inhibition of fatty acid oxidation, and reduction of intestinal glucose absorption (144, 145). Precise mechanism of intracellular action of metformin remains as unknown. Interestingly, 25.9% of patients stopped metformin due to the excessively lost appetite (142). Additionally, 14.1% of patients with overweight or obesity in the metformin group rose either to normal weight or overweight group by weight loss without a diet regimen (142). According to our opinion, the major effect of metformin is an inhibition of appetite. Similar results indicating the beneficial effects on the BMI, BP, FPG, and lipids were also reported (146, 147). Probably the major component of the metabolic syndrome may be the excess fat tissue. So treatment with acarbose plus metformin will probably prevent not only IGT or DM but also the other atherosclerotic endpoints (148).

As a conclusion, hardened RBC-induced capillary endothelial damage terminates with end-organ insufficiencies in early decades in the SCD. Although atherosclerotic endpoints are so common, we detected no case of DM probably due to lower excess fat tissue. As the most common cause of CRD, DM may be a relative insufficiency of pancreas against the excess fat tissue. But the term of excess weight should be replaced with the amount of excess fat tissue in human body since there are approximately 19 kg of excess fat tissue even between the lower and upper borders of normal weight, 33 kg between the lower border of normal weight and obesity, and 66 kg between the lower border of normal weight and morbid obesity in adults.

## References


1. Widlansky ME, Gokce N, Keaney JF Jr, Vita JA. The clinical implications of endothelial dysfunction. J Am Coll Cardiol 2003; 42(7): 1149-60.
2. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2005; 365(9468): 1415-28.
3. Franklin SS, Barboza MG, Pio JR, Wong ND. Blood pressure categories, hypertensive subtypes, and the metabolic syndrome. J Hypertens 2006; 24(10): 2009-16.
4. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002; 106(25): 3143-421.
5. Helvaci MR, Aydin LY, Aydin Y. Digital clubbing may be an indicator of systemic atherosclerosis even at microvascular level. HealthMED 2012; 6(12): 3977-81.
6. Anderson RN, Smith BL. Deaths: leading causes for 2001. Natl Vital Stat Rep 2003; 52(9): 1-85.
7. Helvaci MR, Gokce C, Davran R, Akkucuk S, Ugur M, Oruc C. Mortal quintet of sickle cell diseases. Int J Clin Exp Med 2015; 8(7): 11442-8.
8. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med 1994; 330(23): 1639-44.
9. Helvaci MR, Yaprak M, Abyad A, Pocock L. Atherosclerotic background of hepatosteatosis in sickle cell diseases. World Family Med 2018; 16(3): 12-8.
10. Helvaci MR, Kaya H. Effect of sickle cell diseases on height and weight. Pak J Med Sci 2011; 27(2): 361-4.
11. Helvaci MR, Aydin Y, Ayyildiz O. Hydroxyurea may prolong survival of sickle cell patients by decreasing frequency of painful crises. HealthMED 2013; 7(8): 2327-32.
12. Mankad VN, Williams JP, Harpen MD, Manci E, Longenecker G, Moore RB, et al. Magnetic resonance imaging of bone marrow in sickle cell disease: clinical, hematologic, and pathologic correlations. Blood 1990; 75(1): 274-83.
13. Helvaci MR, Aydin Y, Ayyildiz O. Clinical severity of sickle cell anemia alone and sickle cell diseases with thalassemias. HealthMED 2013; 7(7): 2028-33.

14. Fisher MR, Forfia PR, Chamera E, Housten-Harris T, Champion HC, Girgis RE, et al. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. Am J Respir Crit Care Med 2009; 179(7): 615-21.
15. Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2013; 187(4): 347-65.
16. Davies SC, Luce PJ, Win AA, Riordan JF, Brozovic M. Acute chest syndrome in sickle-cell disease. Lancet 1984; 1(8367): 36-8.
17. Vandemergel X, Renneboog B. Prevalence, aetiologies and significance of clubbing in a department of general internal medicine. Eur J Intern Med 2008; 19(5): 325-9.
18. Schamroth L. Personal experience. S Afr Med J 1976; 50(9): 297-300.
19. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med 1999; 341(15): 1097-105.
20. Helvaci MR, Aydin Y, Gundogdu M. Smoking induced atherosclerosis in cancers. HealthMED 2012; 6(11): 3744-9.
21. Ross R. Atherosclerosis--an inflammatory disease. N Engl J Med 1999; 340(2): 115-26.
22. Ridker PM. High-sensitivity C-reactive protein: Potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. Circulation 2001; 103(13): 1813-8.
23. Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. JAMA 1998; 279(18): 1477-82.
24. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. JAMA 1999; 282(22): 2131-5.
25. Zhou B, Wu Y, Yang J, Li Y, Zhang H, Zhao L. Overweight is an independent risk factor for cardiovascular disease in Chinese populations. Obes Rev 2002; 3(3): 147-56.
26. Zhou BF. Effect of body mass index on all-cause mortality and incidence of cardiovascular diseases--report for meta-analysis of prospective studies open optimal cut-off points of body mass index in Chinese adults. Biomed Environ Sci 2002; 15(3): 245-52.
27. Helvaci MR, Kaya H, Yalcin A, Kuvandik G. Prevalence of white coat hypertension in underweight and overweight subjects. Int Heart J 2007; 48(5): 605-13.
28. Heilbronn LK, Ravussin E. Calorie restriction and aging: review of the literature and implications for studies in humans. Am J Clin Nutr 2003; 78(3): 361-9.
29. Sun Z, Lazar MA. Dissociating fatty liver and diabetes. Trends Endocrinol Metab 2013; 24(1): 4-12.
30. Rastogi A, Sakhuja P, Kumar A, Hissar S, Jain A, Gondal R, et al. Steatosis in chronic hepatitis B: prevalence and correlation with biochemical, histologic, viral, and metabolic parameters. Indian J Pathol Microbiol 2011; 54(3): 454-9.
31. Köse D, Erol C, Kaya F, Koplay M, Köksal Y. Development of fatty liver in children with non-Hodgkin lymphoma. Turk J Pediatr 2014; 56(4): 399-403.
32. Aktas E, Uzman M, Yildirim O, Sahin B, Buyukcam F, Aktas B, et al. Assessment of hepatic steatosis on contrast enhanced computed tomography in patients with colorectal cancer. Int J Clin Exp Med 2014; 7(11): 4342-6.
33. Balcik OS, Akdeniz D, Cipil H, Ikizek M, Uysal S, Kosar A, et al. Serum thrombopoietin levels in patients with non-alcoholic fatty liver disease. Saudi Med J 2012; 33(1): 30-3.
34. Çiftci A, Yilmaz B, Köklü S, Yüksel O, Özsoy M, Erden G, et al. Serum levels of nitrate, nitrite and advanced oxidation protein products (AOPP) in patients with nonalcoholic fatty liver disease. Acta Gastroenterol Belg 2015; 78(2): 201-5.
35. Kucukazman M, Ata N, Yavuz B, Dal K, Sen O, Deveci OS, et al. Evaluation of early atherosclerosis markers in patients with nonalcoholic fatty liver disease. Eur J Gastroenterol Hepatol 2013; 25(2): 147-51.
36. Agaç MT, Korkmaz L, Cavusoglu G, Karadeniz AG, Agaç S, Bektas H, et al. Association between nonalcoholic fatty liver disease and coronary artery disease complexity in patients with acute coronary syndrome: a pilot study. Angiology 2013; 64(8): 604-8.
37. Inci MF, Özkan F, Ark B, Vurdem ÜE, Ege MR, Sincer I, et al. Sonographic evaluation for predicting the presence and severity of coronary artery disease. Ultrasound Q 2013; 29(2): 125-30.
38. Öztürk H, Gümrükçüoğlu HA, Yaman M, Akyol A, Öztürk Ş, Akdağ S, et al. Hepatosteatosis and carotid intima-media thickness in patients with myocardial infarction. J Med Ultrason (2001) 2016; 43(1): 77-82.
39. Karasin M, Tokgoz O, Serifoglu I, Oz I, Erdem O. The Doppler ultrasonographic evaluation of hemodynamic changes in hepatic vascular structures in patients with hepatosteatosis. Pol J Radiol 2014; 79: 299-304.
40. Ozbulbul NI, Yurdakul M, Tola M. Does the visceral fat tissue show better correlation with the fatty replacement of the pancreas than with BMI? Eurasian J Med 2010; 42(1): 24-7.
41. Van Geenen EJ, Smits MM, Schreuder TC, van der Peet DL, Bloemena E, Mulder CJ. Nonalcoholic fatty liver disease is related to nonalcoholic fatty pancreas disease. Pancreas 2010; 39(8): 1185-90.
42. Stamm BH. Incidence and diagnostic significance of minor pathologic changes in the adult pancreas at autopsy: a systematic study of 112 autopsies in patients without known pancreatic disease. Hum Pathol 1984; 15(7): 677-83.
43. Lameloise N, Muzzin P, Prentki M, Assimacopoulos-Jeannet F. Uncoupling protein 2: a possible link between fatty acid excess and impaired glucose-induced insulin secretion? Diabetes 2001; 50(4): 803-9.
44. Aubert A, Garnet JM, Hammel P, Levy P, O'Toole D, Ruszniewski P, et al. Diffuse primary fat replacement of the pancreas: an unusual cause of steatorrhea. Gastroenterol Clin Biol 2007; 31(3): 303-6.
45. Chai J, Liu P, Jin E, Su T, Zhang J, Shi K, et al. MRI chemical shift imaging of the fat content of the pancreas

and liver of patients with type 2 diabetes mellitus. Exp Ther Med 2016; 11(2): 476-80.
46. Quintero JHR, Grosser R, Velez GR, Ramos-Santillan VO, Pereira X, Flores FM, et al. Safety and efficacy of roux-en-y gastric bypass in older aged patients. Rev Col Bras Cir 2022; 49: e20223332.
47. Kim MK, Chun HJ, Park JH, Yea DM, Baek KH, Song KH, et al. The association between ectopic fat in the pancreas and subclinical atherosclerosis in type 2 diabetes. Diabetes Res Clin Pract 2014; 106(3): 590-6.
48. Selim Kul, Ayşegül Karadeniz, İhsan Dursun, Sinan Şahin, Ömer Faruk Çırakoğlu, Muhammet Raşit Sayın, et al. Non-Alcoholic Fatty Pancreas Disease is associated with Increased Epicardial Adipose Tissue and Aortic Intima-Media Thickness. Acta Cardiol Sin 2019; 35(2): 118-25.
49. Pezzilli R, Calculli L. Pancreatic steatosis: Is it related to either obesity or diabetes mellitus? World J Diabetes 2014; 5(4): 415-9.
50. Fodor JG, Tzerovska R, Dorner T, Rieder A. Do we diagnose and treat coronary heart disease differently in men and women? Wien Med Wochenschr 2004; 154(17-18): 423-5.
51. Helvaci MR, Aydin LY, Aydin Y. Chronic obstructive pulmonary disease may be one of the terminal end points of metabolic syndrome. Pak J Med Sci 2012; 28(3): 376-9.
52. Helvaci MR, Kayabasi Y, Celik O, Sencan H, Abyad A, Pocock L. Smoking causes a moderate or severe inflammatory process in human body. Am J Biomed Sci & Res 2023; 7(6): 694-702.
53. Grunberg NE, Greenwood MR, Collins F, Epstein LH, Hatsukami D, Niaura R, et al. National working conference on smoking and body weight. Task Force 1: Mechanisms relevant to the relations between cigarette smoking and body weight. Health Psychol 1992; 11: 4-9.
54. Helvaci MR, Camci C, Nisa EK, Ersahin T, Atabay A, Alrawii I, Ture Y, Abyad A, Pocock L. Severity of sickle cell diseases restricts smoking. Ann Med Medical Res 2024; 7: 1074.
55. Walker JF, Collins LC, Rowell PP, Goldsmith LJ, Moffatt RJ, Stamford BA. The effect of smoking on energy expenditure and plasma catecholamine and nicotine levels during light physical activity. Nicotine Tob Res 1999; 1(4): 365-70.
56. Hughes JR, Hatsukami DK. Effects of three doses of transdermal nicotine on post-cessation eating, hunger and weight. J Subst Abuse 1997; 9: 151-9.
57. Miyata G, Meguid MM, Varma M, Fetissov SO, Kim HJ. Nicotine alters the usual reciprocity between meal size and meal number in female rat. Physiol Behav 2001; 74(1-2): 169-76.
58. Froom P, Melamed S, Benbassat J. Smoking cessation and weight gain. J Fam Pract 1998; 46(6): 460-4.
59. Helvaci MR, Kaya H, Gundogdu M. Gender differences in coronary heart disease in Turkey. Pak J Med Sci 2012; 28(1): 40-4.
60. Prescott E, Hippe M, Schnohr P, Hein HO, Vestbo J. Smoking and risk of myocardial infarction in women and men: longitudinal population study. BMJ 1998; 316(7137): 1043-7.
61. Helvaci MR, Kabay S, Gulcan E. A physiologic events' cascade, irritable bowel syndrome, may even terminate with urolithiasis. J Health Sci 2006; 52(4): 478-81.
62. Helvaci MR, Dede G, Yildirim Y, Salaz S, Abyad A, Pocock L. Smoking may even cause irritable bowel syndrome. World Family Med 2019; 17(3): 28-33.
63. Helvaci MR, Algin MC, Kaya H. Irritable bowel syndrome and chronic gastritis, hemorrhoid, urolithiasis. Eurasian J Med 2009; 41(3): 158-61.
64. Kamimura D, Loprinzi PD, Wang W, Suzuki T, Butler KR, Mosley TH, et al. Physical activity is associated with reduced left ventricular mass in obese and hypertensive African Americans. Am J Hypertens 2017; 30(6): 617-23.
65. Parfrey NA, Moore W, Hutchins GM. Is pain crisis a cause of death in sickle cell disease? Am J Clin Pathol 1985; 84(2): 209-12.
66. Helvaci MR, Ayyildiz O, Gundogdu M. Hydroxyurea therapy and parameters of health in sickle cell patients. HealthMED 2014; 8(4): 451-6.
67. Helvaci MR, Tonyali O, Yaprak M, Abyad A, Pocock L. Increased sexual performance of sickle cell patients with hydroxyurea. World Family Med 2019; 17(4): 28-33.
68. Helvaci MR, Aydin Y, Aydin LY, Sevinc A, Camci C, Abyad A, Pocock L. Red blood cell transfusions should be preserved just for emergencies in sickle cell diseases. World Family Med 2025; 23(4): 40-53.
69. Helvaci MR, Atci N, Ayyildiz O, Muftuoglu OE, Pocock L. Red blood cell supports in severe clinical conditions in sickle cell diseases. World Family Med 2016; 14(5): 11-8.
70. Helvaci MR, Ayyildiz O, Gundogdu M. Red blood cell transfusions and survival of sickle cell patients. HealthMED 2013; 7(11): 2907-12.
71. Helvaci MR, Cayir S, Halici H, Sevinc A, Camci C, Abyad A, Pocock L. Red blood cell transfusions may have the strongest analgesic effect during acute painful crises in sickle cell diseases. Ann Clin Med Case Rep 2024; V13(12): 1-12.
72. Miller ST, Sleeper LA, Pegelow CH, Enos LE, Wang WC, Weiner SJ, et al. Prediction of adverse outcomes in children with sickle cell disease. N Engl J Med 2000; 342(2): 83-9.
73. Balkaran B, Char G, Morris JS, Thomas PW, Serjeant BE, Serjeant GR. Stroke in a cohort of patients with homozygous sickle cell disease. J Pediatr 1992; 120(3): 360-6.
74. Cole TB, Sprinkle RH, Smith SJ, Buchanan GR. Intravenous narcotic therapy for children with severe sickle cell pain crisis. Am J Dis Child 1986; 140(12): 1255-9.
75. Yawn BP, Buchanan GR, Afenyi-Annan AN, Ballas SK, Hassell KL, James AH, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA 2014; 312(10): 1033-48.
76. Miller BA, Platt O, Hope S, Dover G, Nathan DG. Influence of hydroxyurea on fetal hemoglobin production in vitro. Blood 1987; 70(6): 1824-9.
77. Platt OS. Is there treatment for sickle cell anemia? N Engl J Med 1988; 319(22): 1479-80.

78. Helvaci MR, Aydogan F, Sevinc A, Camci C, Dilek I. Platelet and white blood cell counts in severity of sickle cell diseases. HealthMED 2014; 8(4): 477-82.
79. Charache S. Mechanism of action of hydroxyurea in the management of sickle cell anemia in adults. Semin Hematol 1997; 34(3): 15-21.
80. Charache S, Barton FB, Moore RD, Terrin ML, Steinberg MH, Dover GJ, et al. Hydroxyurea and sickle cell anemia. Clinical utility of a myelosuppressive "switching" agent. The Multicenter Study of Hydroxyurea in Sickle Cell Anemia. Medicine (Baltimore) 1996; 75(6): 300-26.
81. Steinberg MH, Barton F, Castro O, Pegelow CH, Ballas SK, Kutlar A, et al. Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment. JAMA 2003; 289(13): 1645-51.
82. Lebensburger JD, Miller ST, Howard TH, Casella JF, Brown RC, Lu M, et al; BABY HUG Investigators. Influence of severity of anemia on clinical findings in infants with sickle cell anemia: analyses from the BABY HUG study. Pediatr Blood Cancer 2012; 59(4): 675-8.
83. Toghi H, Konno S, Tamura K, Kimura B, Kawano K. Effects of low-to-high doses of aspirin on platelet aggregability and metabolites of thromboxane A2 and prostacyclin. Stroke 1992; 23(10): 1400-3.
84. Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009; 373(9678): 1849-60.
85. Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. Lancet Oncol 2012; 13(5): 518-27.
86. Macdonald S. Aspirin use to be banned in under 16 year olds. BMJ 2002; 325(7371): 988.
87. Schrör K. Aspirin and Reye syndrome: a review of the evidence. Paediatr Drugs 2007; 9(3): 195-204.
88. Pugliese A, Beltramo T, Torre D. Reye's and Reye's-like syndromes. Cell Biochem Funct 2008; 26(7): 741-6.
89. Hurwitz ES. Reye's syndrome. Epidemiol Rev 1989; 11: 249-53.
90. Meremikwu MM, Okomo U. Sickle cell disease. BMJ Clin Evid 2011; 2011: 2402.
91. Mohamed S, Fong CM, Ming YJ, Kori AN, Wahab SA, Ali ZM. Evaluation of an initiation regimen of warfarin for international normalized ratio target 2.0 to 3.0. J Pharm Technol 2021; 37(6): 286-92.
92. Chu MWA, Ruel M, Graeve A, Gerdisch MW, Ralph J, Damiano Jr RJ, Smith RL. Low-dose vs standard warfarin after mechanical mitral valve replacement: A randomized trial. Ann Thorac Surg 2023; 115(4): 929-38.
93. Crowther MA, Douketis JD, Schnurr T, Steidl L, Mera V, Ultori C, et al. Oral vitamin K lowers the international normalized ratio more rapidly than subcutaneously vitamin K in the treatment of warfarin-associated coagulopathy. A randomized, controlled trial. Ann Intern Med 2002; 137(4): 251-4.
94. Brown DG, Wilkerson EC, Love WE. A review of traditional and novel oral anticoagulant and antiplatelet therapy for dermatologists and dermatologic surgeons. J Am Acad Dermatol 2015; 72(3): 524-34.
95. Delaney JA, Opatrny L, Brophy JM, Suissa S. Drug drug interactions between antithrombotic medications and the risk of gastrointestinal bleeding. CMAJ 2007; 177(4): 347-51.
96. Dahal K, Kunwar S, Rijal J, Schulman P, Lee J. Stroke, major bleeding, and mortality outcomes in warfarin users with atrial fibrillation and chronic kidney disease: a meta-analysis of observational studies. Chest 2016; 149(4): 951-9.
97. Chai-Adisaksopha C, Lorio A, Hillis C, Siegal D, Witt DM, Schulman S, et al. Warfarin resumption following anticoagulant-associated intracranial hemorrhage: A systematic review and meta-analysis. Thromb Res 2017; 160: 97-104.
98. Ferro JM, Coutinho JM, Dentali F, Kobayashi A, Alasheev A, Canhao P, et al. Safety and efficacy of dabigatran etexilate vs dose-adjusted warfarin in patients with cerebral venous thrombosis: A randomized clinical trial. JAMA Neurol 2019; 76(12): 1457-65.
99. Meade TW. Low-dose warfarin and low-dose aspirin in the primary prevention of ischemic heart disease. Am J Cardiol 1990; 65(6): 7C-11C.
100. Singer DE, Hughes RA, Gress DR, Sheehan MA, Oertel LB, Maraventano SW, et al. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. N Engl J Med 1990; 323(22): 1505-11.
101. Levine M, Hirsh J, Gent M, Arnold A, Warr D, Falanya A, et al. Double-blind randomised trial of a very-low-dose warfarin for prevention of thromboembolism in stage IV breast cancer. Lancet 1994; 343(8902): 886-9.
102. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014; 383(9921): 955-62.
103. Vinogradova Y, Coupland C, Hill T, Hippisley-Cox J. Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care. BMJ 2018; 362: k2505.
104. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361(12): 1139-51.
105. Helvaci MR, Cayir S, Halici H, Sevinc A, Camci C, Abyad A, Pocock L. Terminal endpoints of systemic atherosclerotic processes in sickle cell diseases. World Family Med 2024; 22(5): 13-23.
106. Helvaci MR, Daglioglu MC, Halici H, Sevinc A, Camci C, Abyad A, Pocock L. Low-dose aspirin plus low-dose warfarin may be the standard treatment regimen in Buerger's disease. World Family Med 2024; 22(6): 22-35.
107. Helvaci MR, Erden ES, Aydin LY. Atherosclerotic background of chronic obstructive pulmonary disease in sickle cell patients. HealthMED 2013; 7(2): 484-8.
108. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. Lancet 2009; 374(9691): 733-43.

109. Schoepf D, Heun R. Alcohol dependence and physical comorbidity: Increased prevalence but reduced relevance of individual comorbidities for hospital-based mortality during a 12.5-year observation period in general hospital admissions in urban North-West England. Eur Psychiatry 2015; 30(4): 459-68.
110. Singh G, Zhang W, Kuo YF, Sharma G. Association of Psychological Disorders With 30-Day Readmission Rates in Patients With COPD. Chest 2016; 149(4): 905-15.
111. Mannino DM, Watt G, Hole D, Gillis C, Hart C, McConnachie A, et al. The natural history of chronic obstructive pulmonary disease. Eur Respir J 2006; 27(3): 627-43.
112. Mapel DW, Hurley JS, Frost FJ, Petersen HV, Picchi MA, Coultas DB. Health care utilization in chronic obstructive pulmonary disease. A case-control study in a health maintenance organization. Arch Intern Med 2000; 160(17): 2653-58.
113. Anthonisen NR, Connett JE, Enright PL, Manfreda J; Lung Health Study Research Group. Hospitalizations and mortality in the Lung Health Study. Am J Respir Crit Care Med 2002; 166(3): 333-9.
114. McGarvey LP, John M, Anderson JA, Zvarich M, Wise RA; TORCH Clinical Endpoint Committee. Ascertainment of cause-specific mortality in COPD: operations of the TORCH Clinical Endpoint Committee. Thorax 2007; 62(5): 411-5.
115. Trent JT, Kirsner RS. Leg ulcers in sickle cell disease. Adv Skin Wound Care 2004: 17(8); 410-6.
116. Minniti CP, Eckman J, Sebastiani P, Steinberg MH, Ballas SK. Leg ulcers in sickle cell disease. Am J Hematol 2010; 85(10): 831-3.
117. Myers KA, Farquhar DR. The rational clinical examination. Does this patient have clubbing? JAMA 2001; 286(3): 341-7.
118. Toovey OT, Eisenhauer HJ. A new hypothesis on the mechanism of digital clubbing secondary to pulmonary pathologies. Med Hypotheses 2010; 75(6): 511-3.
119. Nassiri AA, Hakemi MS, Asadzadeh R, Faizei AM, Alatab S, Miri R, et al. Differences in cardiovascular disease risk factors associated with maximum and mean carotid intima-media thickness among hemodialysis patients. Iran J Kidney Dis 2012; 6(3): 203-8.
120. Helvaci MR, Gokce C, Sahan M, Hakimoglu S, Coskun M, Gozukara KH. Venous involvement in sickle cell diseases. Int J Clin Exp Med 2016; 9(6): 11950-7.
121. Xia M, Guerra N, Sukhova GK, Yang K, Miller CK, Shi GP, et al. Immune activation resulting from NKG2D/ligand interaction promotes atherosclerosis. Circulation 2011; 124(25): 2933-43.
122. Hall JE, Henegar JR, Dwyer TM, Liu J, da Silva AA, Kuo JJ, et al. Is obesity a major cause of chronic kidney disease? Adv Ren Replace Ther 2004; 11(1): 41-54.
123. Nerpin E, Ingelsson E, Risérus U, Helmersson-Karlqvist J, Sundström J, Jobs E, et al. Association between glomerular filtration rate and endothelial function in an elderly community cohort. Atherosclerosis 2012; 224(1): 242-6.
124. Stengel B, Tarver-Carr ME, Powe NR, Eberhardt MS, Brancati FL. Lifestyle factors, obesity and the risk of chronic kidney disease. Epidemiology 2003; 14(4): 479-87.
125. Bonora E, Targher G. Increased risk of cardiovascular disease and chronic kidney disease in NAFLD. Nat Rev Gastroenterol Hepatol 2012; 9(7): 372-81.
126. Helvaci MR, Cayir S, Halici H, Sevinc A, Camci C, Sencan H, Davran R, Abyad A, Pocock L. Acute chest syndrome and coronavirus disease may actually be genetically determined exaggerated immune response syndromes particularly in pulmonary capillaries. World Family Med 2024; 22(3): 6-16.
127. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, et al. Chronic kidney disease and mortality risk: a systematic review. J Am Soc Nephrol 2006; 17(7): 2034-47.
128. Helvaci MR, Aydin Y, Aydin LY. Atherosclerotic background of chronic kidney disease in sickle cell patients. HealthMED 2013; 7(9): 2532-7.
129. DeBaun MR, Gordon M, McKinstry RC, Noetzel MJ, White DA, Sarnaik SA, et al. Controlled trial of transfusions for silent cerebral infarcts in sickle cell anemia. N Engl J Med 2014; 371(8): 699-710.
130. Majumdar S, Miller M, Khan M, Gordon C, Forsythe A, Smith MG, et al. Outcome of overt stroke in sickle cell anaemia, a single institution's experience. Br J Haematol 2014; 165(5): 707-13.
131. Kossorotoff M, Grevent D, de Montalembert M. Cerebral vasculopathy in pediatric sickle-cell anemia. Arch Pediatr 2014; 21(4): 404-14.
132. Charache S, Terrin ML, Moore RD, Dover GJ, Barton FB, Eckert SV, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. N Engl J Med 1995; 332(20): 1317-22.
133. Rosak C, Mertes G. Critical evaluation of the role of acarbose in the treatment of diabetes: patient considerations. Diabetes Metab Syndr Obes 2012; 5: 357-67.
134. Salvatore T, Giugliano D. Pharmacokinetic-pharmacodynamic relationships of acarbose. Clin Pharmacokinet 1996; 30(2): 94-106.
135. DiNicolantonio JJ, Bhutani J, O'Keefe JH. Acarbose: safe and effective for lowering postprandial hyperglycaemia and improving cardiovascular outcomes. Open Heart 2015; 2(1): e000327.
136. Leonhardt W, Hanefeld M, Fischer S, Schulze J. Efficacy of alpha-glucosidase inhibitors on lipids in NIDDM subjects with moderate hyperlipidaemia. Eur J Clin Invest 1994; 24(3): 45-9.
137. Li FF, Fu LY, Xu XH, Su XF, Wu JD, Ye L, et al. Analysis of the add-on effect of alpha-glucosidase inhibitor, acarbose in insulin therapy: A pilot study. Biomed Rep 2016; 5(4): 461-6.
138. Standl E, Schnell O, Ceriello A. Postprandial hyperglycemia and glycemic variability: should we care? Diabetes Care 2011; 34(2): 120-7.

139. Helvaci MR, Halici H, Erdogan K, Sevinc A, Camci C, Abyad A, Pocock L. Acarbose in the treatment of chronic obstructive pulmonary disease. World Family Med 2025; 23(2): 37-52.
140. Wettergreen SA, Sheth S, Malveaux J. Effects of the addition of acarbose to insulin and non-insulin regimens in veterans with type 2 diabetes mellitus. Pharm Pract (Granada) 2016; 14(4): 832.
141. Van De Laar FA, Lucassen PL, Akkermans RP, Van de Lisdonk EH, Rutten GE, Van Weel C. Alpha-glucosidase inhibitors for patients with type 2 diabetes: results from a Cochrane systematic review and meta-analysis. Diabetes Care 2005; 28(1): 154-63.
142. Helvaci MR, Kaya H, Borazan A, Ozer C, Seyhanli M, Yalcin A. Metformin and parameters of physical health. Intern Med 2008; 47(8): 697-703.
143. Helvaci MR, Aydin Y, Varan G, Abyad A, Pocock L. Acarbose versus metformin in the treatment of metabolic syndrome. World Family Med 2018; 16(5): 10-15.
144. Stumvoll M, Nurjhan N, Perriello G, Dailey G, Gerich JE. Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. N Engl J Med 1995; 333(9): 550-554.
145. Jackson RA, Hawa MI, Jaspan JB, Sim BM, Disilvio L, Featherbe D, et al. Mechanism of metformin action in non-insulin-dependent diabetes. Diabetes 1987; 36(5): 632-640.
146. Campbell IW, Howlett HC. Worldwide experience of metformin as an effective glucose-lowing agent: a meta-analysis. Diabetes Metab Rev 1995; 11(1): 57-62.
147. Helvaci MR, Kurt GD, Halici H, Sevinc A, Camci C, Abyad A, Pocock L. Metformin in the treatment of chronic renal disease. World Family Med 2025; 23(1): 12-27.
148. Helvaci MR, Helvaci E, Helvaci E, Aydin Y, Aydin LY, Sevinc A, Camci C, Abyad A, Pocock L. Weight loss with acarbose and metformin may be curative in early phases of diabetes mellitus. J Clin Gastro Hepatol Res 2025; 7(2): 150.