Middle East Journal of Internal Medicine

ISSN 1837 9052

December 2020 - Volume 12, Issue3

From the Editor

Ahmad Husari *(Chief Editor)*
Email: editor@me-jim.com

This the last issue this year for the journal. We would like to send a special thanks for the authors that submitted papers to the journal, our readers, reviewers and production staff headed by our publishing manager and the editorial office.

Almubarak et al., report an interesting case of Small Cell Cancer of the Parotid Gland. The authors stressed that salivary gland small cell carcinomas (SmCC) are extremely rare and metastasis from lung only being reported in select case studies. This is a case of parotid gland SmCC and lung SmCC. The pulmonary mass may represent metastasis from the parotid tumor. However, a new lung primary could not be excluded. A synchronous primary lung SmCC appears to be more likely.

Helvaci et al., stressed that Triglycerides may be acute phase reactants which are not negatively affected by pathologic weight loss. They pointed that Sickle cell diseases (SCD) are chronic inflammatory process on vascular endothelium terminating with atherosclerosis induced end-organ failures in early decades of life. Consecutive patients with the SCD and controls were studied. The study included 363 patients with the SCD (169 females) and 255 age and gender-matched controls (119 females). Mean ages of the SCD patients were similar in males and females (31.1 versus 31.0 years, respectively, $p>0.05$). Although the body weight and body mass index (BMI) were significantly retarded in the SCD patients (59.9 versus 71.5 kg and 21.9 versus 25.6 kg/m2, respectively, $p= 0.000$ for both), the body heights were similar in both groups (164.9 versus 167.0 cm, $p>0.05$). Parallel to the retarded body weight, fasting plasma glucose (92.8 versus 97.6 mg/dL, $p= 0.005$), total cholesterol (121.4 versus 165.0 mg/dL, $p= 0.000$), low density lipoproteins (70.4 versus 102.4 mg/dL, $p= 0.000$), high density lipoproteins (26.0 versus 39.6 mg/dL, $p= 0.000$), systolic blood pressures (BP) (115.2 versus 122.6 mmHg, $p= 0.000$), and diastolic BP (73.0 versus 86.6 mmHg, $p= 0.000$) were all lower in the SCD patients, significantly. Interestingly, only the triglycerides (TG) value was higher in the SCD patients (129.4 versus 117.3 mg/dL, $p= 0.000$), significantly. Similarly, the alanine aminotransferase value was not suppressed in the SCD patients, too (27.4 versus 27.3 U/L, respectively, $p>0.05$). The authors concluded that plasma TG may be acute phase reactants indicating disseminated endothelial injury and accelerated atherosclerosis all over the body, and their plasma values are not negatively affected by pathologic weight loss.

Helvaci et al., stressed that total bilirubin value of the plasma may have prognostic significance in sickle cell diseases (SCD). All patients with the SCD were included between March 2007 and June 2016. They studied 253 patients (128 females) with a plasma bilirubin value of lower than 5.0 mg/dL and 109 patients (43 females) with a value of 5.0 mg/dL and higher. There were 31 deaths during the ten-year period (14 females with a mean age of 33.3 and 17 males with a mean age of 30.2 years, $p>0.05$). Although the similar mean ages (30.2 versus 31.7 years, $p>0.05$), male ratio (60.5% versus 49.4%, $p<0.05$), ileus (3.9% versus 10.0%, $p<0.01$), digital clubbing (6.3% versus 26.6%, $p<0.001$), leg ulcers (12.2% versus 20.1%, $p<0.05$), pulmonary hypertension (9.4% versus 23.8%, $p<0.001$), cirrhosis (1.5% versus 15.5%, $p<0.001$), chronic renal disease (CRD) (6.7% versus 12.8%, $p<0.05$), and exitus (4.7% versus 11.9%, $p<0.001$) were all higher in patients with the plasma bilirubin value of 5.0 mg/dL and higher. The authors concluded that SCD are severe inflammatory processes on vascular endothelium, particularly at the capillary level and terminate with an accelerated atherosclerosis induced end-organ failures in early years of life. Total bilirubin value of the plasma may have prognostic significance due to the higher prevalences of ileus, digital clubbing, leg ulcers, pulmonary hypertension, cirrhosis, CRD, and exitus in patients with the plasma bilirubin value of 5.0 mg/dL and higher. The higher bilirubin values may either show the severity of hemolytic process initiated at birth or an advanced hepatic involvement in such cases.

A paper from Lebanon reviewed the overall strategies for management of Parkinson disease. It is part five of a series of papers on Parkinson disease. The author stressed that Parkinson's disease has a wide variety of motor and non-motor symptoms. Treatment aims to control the patient's symptoms by replenishing the dopaminergic system with levodopa or dopamine agonists. Monoamine oxidase B inhibitors are also effective first-line drugs. Keeping symptoms under continual control early in the course of the disease may have beneficial effects as Parkinson's disease progresses. Therapy is tailored to each patient's response to the drugs and their ability to tolerate them. Limited responses of motor and many non- motor symptoms may require the addition of other treatments. The adverse effects of drugs used in the treatment of Parkinson's disease are usually reversible. As the disease progresses and problems accumulate, deep brain stimulation (DBS) surgery may be a reasonable therapeutic option for some individuals, although many people with PD do not qualify for DBS for a variety of reasons. In addition nonpharmacological alternatives are helpful , including diet, exercise and occupational therapy. However, the majority of people with PD can lead full and active lives with good symptom control for many years.

Small Cell Cancer of the Parotid Gland

Hassan Almubarak (1)
Awad Alsamghan (2)
Mohammed Abadi Al-Saleem (2)
Eisa Yazeed Ghazwani (3)
Safar Abadi Al-Saleem (2)

(1) Division of Radiology, Department of Internal Medicine, College of Medicine, King Khalid University, Abha, Kingdom of Saudi Arabia
(2) Department of Family & Community Medicine, College of Medicine, King Khalid University, Abha, Kingdom of Saudi Arabia
(3) Department of Family & Community Medicine, Faculty of Medicine, Najran University, Najran, Kingdom of Saudi Arabia

Corresponding author:
Dr. Awad S. Alsamghan
Department of Family & Community Medicine,
College of Medicine, King Khalid University, Abha,
Kingdom of Saudi Arabia
Email: awadalsamghan@gmail.com

Received September 2020. Accepted October 2020. Published December 1, 2020.
Please cite this article as: Hassan Almubarak et al. Small Cell Cancer of the Parotid Gland. Middle East J Intern Med 2020; 13(3): 3-6.
DOI: 10.5742/MEJIM2020.93791

ABSTRACT

Salivary gland small cell carcinomas (SmCC) are extremely rare and metastasis from lung only being reported in select case studies. This is a case of parotid gland SmCC and lung SmCC. The pulmonary mass may represent metastasis from the parotid tumor. However, a new lung primary could not be excluded. A synchronous primary lung SmCC appears to be more likely.

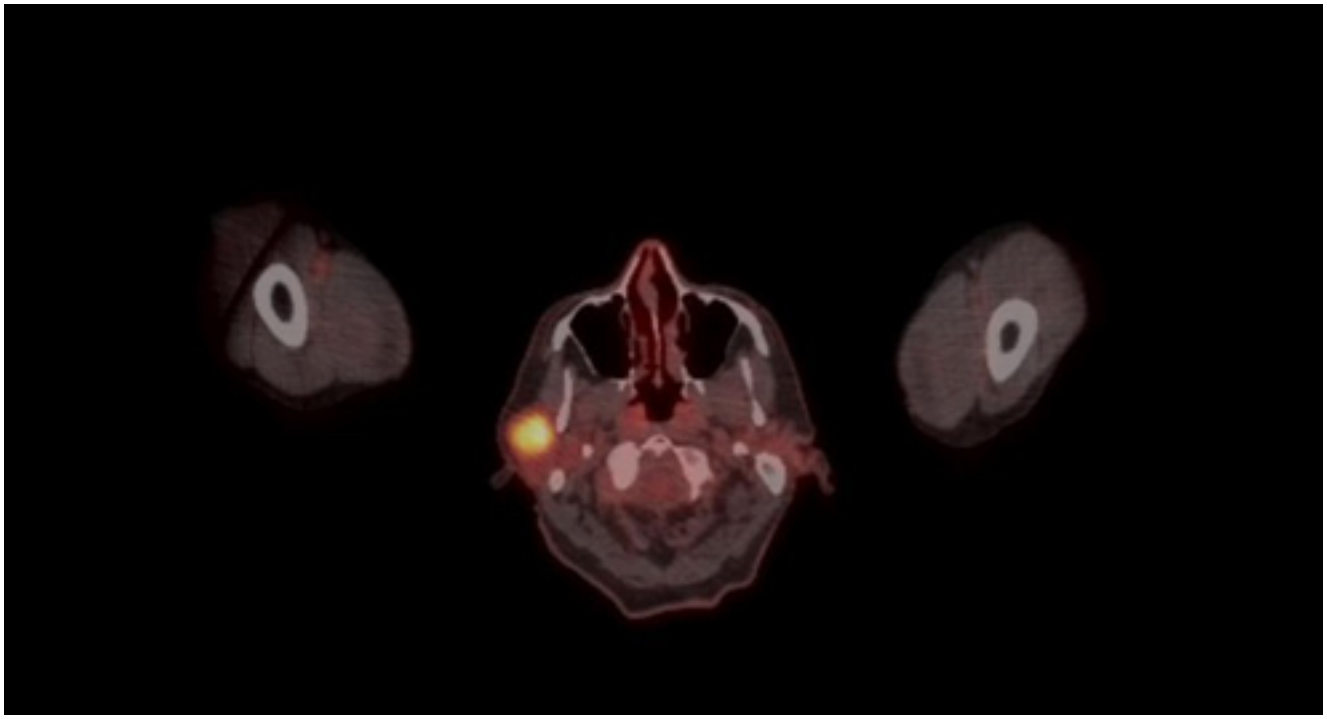
Introduction

Salivary gland small cell carcinomas (SmCC) are sporadic with primaries accounting for less than 1% of salivary gland tumors with bad prognosis [1,2] and metastasis from lung is only being reported in select case studies [3]. Often these are classified into neuroendocrine or ductal carcinomas [4]. This is a case of parotid gland SmCC and lung SmCC.

Case Report

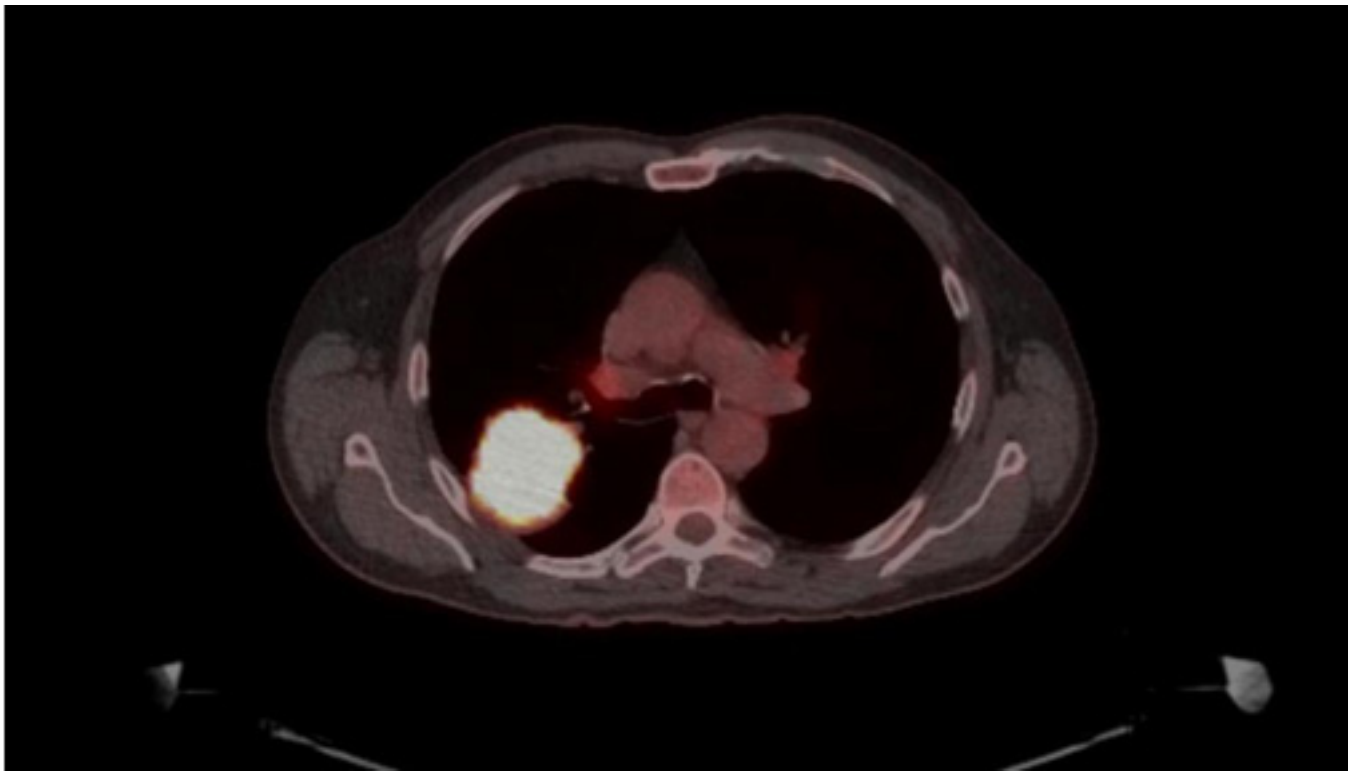
A 73-year-old gentleman presented with a lump over his right parotid gland region, which had grown over 10 months. The initial fine needle aspiration (FNA) at 4 months was negative. However, a second FNA showed atypical small cells and abundant lymphocytes, consistent with SmCC. On subsequent staging FDG PET, a soft tissue mass of 3 cm within the right parotid gland was identified with intense FDG uptake (Figure 1).

Figure 1



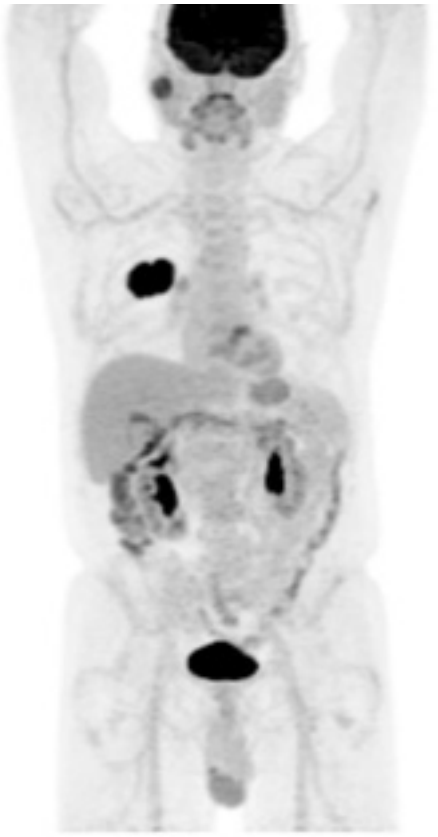
The patient was a former heavy smoker with a 110 pack-year history and a positive family history for lung cancer and on FDG PET staging, a highly hypermetabolic mass of 7 cm was also identified in the right lung (Figure 2).

Figure 2



The lung biopsy showed similar histological features to the parotid. Based on the pathologist's opinion, the lung mass may represent a metastasis from the parotid tumor. However, a new lung primary could not be totally excluded. Maximum-intensity projection (MIP) 18F-FDG PET of the parotid gland and lung FDG activity shows similar high metabolic activities in both right parotid and right lung mass (Figure 3).

Figure 3



Discussion

SmCC of the parotid gland has only been presented in select cases and typically presents in the lung; since the parotid is an unlikely area for a SmCC primary [5], it is important to exclude the possibility of a metastases.

Based on the limited case reports of this malignancy, patients generally present with a progressively enlarging neck mass followed by FNA biopsy and subsequent metastatic work-up.

Based on the case reports, SmCC is typically highly FDG avid. The FDG metabolic imaging parameters can differentiate benign and malignant tumor uptake in parotid glands. There are four levels of FDG uptake in parotid glands: normal physiologic uptake, increased diffuse uptake, benign tumor uptake, and malignant tumor uptake. The FDG metabolic imaging parameters can differentiate benign and malignant tumor uptake in parotid glands [6].

On MRI images, the tumor typically demonstrates circumscribed and heterogeneous enhancement on gadolinium-enhanced T1-weighted images. Specific signs predictive of malignancy are T2 hypointensity of the parotid tumor, ill-defined margins, diffuse growth, infiltration of subcutaneous tissue, and lymphadenopathy [7]. Tumor size appears to be the most important prognostic factor [8].

As this patient demonstrated a second lesion in the lung it is difficult to determine the patient's specific prognosis. Small cell lung cancer (SCLC) is staged into two categories; limited stage indicates SCLC is only located on one side of the chest and can be treated by radiation and chemotherapy and rarely, by surgery. While the other stage, termed extensive stage, means that SCLC has spread throughout the lung to the lymph nodes or has metastasised to other parts of the body [9].

It is helpful to note that the prognosis of primary SmCC of salivary glands appears to be more favorable than those found in other areas with a 5-year survival of 46% (compared to lung with 31% or less obviously based on the stage) [10]. Ultimately, the treatment consists of a combination of surgery followed by chemotherapy and radiation [11].

Conclusions

Small cell carcinoma is primarily a pulmonary neoplasm that rarely arises in extrapulmonary sites, including salivary glands of the head and neck. Our case is a 73-year-old man who presented with right parotid SmCC and mass in the right lung of similar histological features to the parotid lesion. The pulmonary mass may represent a metastasis from the parotid tumour, however a new lung primary could not be excluded. Based on the intensity of the parotid gland and lung FDG activity, a primary lung SmCC as a synchronous cancer appears to be more likely. We still need more cases and may be case series similar to this report to have a better understanding.

References

1. Altinay, S., Firat, P., Yalcin, S., Taskin,: Primary small cell carcinoma of the parotid: Fine needle aspiration and immunohistochemical features of a neuroendocrine variant. Journal of Cytology. 33:34-36.

2. Koss LG, Spiro RH, Hajdu S. Small cell (oat cell) carcinoma of minor salivary gland origin. Cancer. 1972;30:737–41

3. Baca, J.M., Chiara, et al.: Small-Cell Carcinoma of the Parotid Gland. Journal of Clinical Oncology. 29:34-36.

4. Kraemer, B.B., MacKay, B., Batsakis, J.G.: Small Cell Carcinomas of the Parotid Gland. Cancer Small. 52:2115-2121. 10.1002/1097-0142(19831201)52:11<2115::aid-cncr2820521124>3.0.co;2-z

5. Kim JH, Lee SH, Park J, Kim HY, Lee SI, Nam EM, et al. Extrapulmonary small-cell carcinoma: A single-institution experience. Jpn J Clin Oncol. 2004;34:250–4.

6. David Hadiprodjo, Timothy Ryan, Minh-Tam Truong, Gustavo Mercier, and Rathan M. Subramaniam: American Journal of Roentgenology. 2012;198: W185-W190. 10.2214/AJR.11.7172

7. A. Christe, C. Waldherr, R. Hallett, P. Zbaeren and H. Thoeny: American Journal of Neuroradiology August 2011, 32 (7) 1202-1207

8. Nagao T, Gaffey TA, Olsen KD, Serizawa H, Lewis JE. Small cell carcinoma of the major salivary glands: Clinicopathologic study with emphasis on cytokeratin 20 immunoreactivity and clinical outcome. Am J Surg Pathol. 2004;28:762–70.

9. Jan P. Van Meerbeeck; Dean A. Fennell; Dirk K.M. De Ruysscher: Small-cell lung cancer. The Lancet. 2011, 9804:1741-1755. doi.org/10.1016/S0140-6736(11)60165-7

10. Gnepp, D.R., Corio, R.L., Brannon, R.B.: Small Cell Carcinoma of the Major Salivary Glands. Cancer. 58:705-714. 10.1002/1097-0142(19860801)58:3<705::aid-cncr2820580318>3.0.co;2-t.

11. Henke, A.C., Cooley, et al.: Fine-Needle Aspiration Cytology of Cell Carcinoma of the Parotid. Diagnostic Cytopathology. 25:126-129. 10.4103/0970-9371.175509

Prognostic significance of plasma bilirubin in sickle cell diseases

Mehmet Rami Helvaci (1)
Atilla Yalcin (1)
Zeki Arslanoglu (2)
Mehmet Duru (3)
Abdulrazak Abyad (4)
Lesley Pocock (5)

(1) Specialist of Internal Medicine, MD
(2) Specialist of Dentistry, Ph
(3) Specialist of Emergency Medicine, MD
(4) Middle-East Academy for Medicine of Aging, MD
(5) medi+WORLD International

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

Received September 2020. Accepted October 2020. Published December 1, 2020.
Please cite this article as: Mehmet Rami Helvaci et al. Prognostic significance of plasma bilirubin in sickle cell diseases. Middle East J Intern Med 2020; 13(3): 7-13 DOI: 10.5742/MEJIM2020.93792

ABSTRACT

Background: Total bilirubin value of the plasma may have prognostic significance in sickle cell diseases (SCD).

Methods: All patients with the SCD were included between March 2007 and June 2016.

Results: We studied 253 patients (128 females) with a plasma bilirubin value of lower than 5.0 mg/dL and 109 patients (43 females) with a value of 5.0 mg/dL and higher. There were 31 deaths during the ten-year period (14 females with a mean age of 33.3 and 17 males with a mean age of 30.2 years, $p>0.05$). Although the similar mean ages (30.2 versus 31.7 years, $p>0.05$), male ratio (60.5% versus 49.4%, $p<0.05$), ileus (3.9% versus 10.0%, $p<0.01$), digital clubbing (6.3% versus 26.6%, $p<0.001$), leg ulcers (12.2% versus 20.1%, $p<0.05$), pulmonary hypertension (9.4% versus 23.8%, $p<0.001$), cirrhosis (1.5% versus 15.5%, $p<0.001$), chronic renal disease (CRD) (6.7% versus 12.8%, $p<0.05$), and exitus (4.7% versus 11.9%, $p<0.001$) were all higher in patients with the plasma bilirubin value of 5.0 mg/dL and higher.

Conclusion: SCD are severe inflammatory processes on vascular endothelium, particularly at the capillary level and terminate with accelerated atherosclerosis induced end-organ failures in early years of life. Total bilirubin value of the plasma may have prognostic significance due to the higher prevalence of ileus, digital clubbing, leg ulcers, pulmonary hypertension, cirrhosis, CRD, and exitus in patients with the plasma bilirubin value of 5.0 mg/dL and higher. The higher bilirubin values may either show the severity of hemolytic process initiated at birth or an advanced hepatic involvement in such cases.

Key words: Sickle cell diseases, plasma bilirubin, chronic endothelial damage, accelerated atherosclerosis, end-organ failure, metabolic syndrome, early aging

Introduction

Chronic endothelial damage may be the leading cause of aging by causing disseminated tissue hypoxia all over the body. Probably whole afferent vasculature including capillaries are mainly involved in the process since much higher blood pressures (BP) of the afferent vasculature may be the major underlying cause by inducing recurrent endothelial injuries. Thus the term of venosclerosis is not as famous as atherosclerosis in the literature. Secondary to the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls become thickened, their lumens are narrowed, and they lose their elastic nature which reduces blood flow and increases systolic BP further. Some of the well-known accelerators of the atherosclerotic process are sedentary lifestyle, physical inactivity, excess weight, smoking, alcohol, cancers, and chronic inflammatory and infectious processes including sickle cell diseases (SCD), rheumatologic disorders, and tuberculosis for the development of irreversible endpoints including obesity, hypertension (HT), diabetes mellitus (DM), peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), pulmonary hypertension, chronic renal disease (CRD), coronary heart disease (CHD), cirrhosis, osteoporosis, and stroke, all of which terminate with early aging and premature death. They were discussed under the titles of metabolic syndrome, aging sydrome, and accelerated endothelial damage syndrome in the literature, extensively (1, 2). Although early withdrawal of the causative factors may delay terminal endpoints, the endothelial changes cannot be reversed completely after the development of obesity, HT, DM, PAD, COPD, pulmonary hypertension, CRD, CHD, or stroke due to their fibrotic nature (3, 4). Similarly, SCD are severe inflammatory processes on vascular endothelium, particularly at the capillary level and terminate with accelerated atherosclerosis induced end-organ failures in early years of life. Total bilirubin value of the plasma may have prognostic significance in 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 into the study. The SCD are diagnosed with hemoglobin electrophoresis performed via high performance liquid chromatography. Medical histories including transfused units of red blood cells (RBC) in their lives, surgical operations, medical emergencies, leg ulcers, and stroke were learnt. A complete physical examination was performed by the same internist. Body weight and height were measured, and body mass index (BMI) of each case was calculated by the Same Physician instead of verbal expressions. Weight in kilograms is divided by height in meters squared (5). Patients with disseminated teeth loss (<20 teeth present) were detected. Digital clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter which is greater than 1.0, and with the presence of Schamroth's sign (6, 7). Cases with acute painful crisis or any other inflammatory event were treated at first, and the laboratory tests and clinical measurements were performed on the silent phase. Check up procedures including serum creatinine, liver function tests, total bilirubin value, markers of hepatitis viruses A, B, C and human immunodeficiency virus, a posterior-anterior chest x-ray film, an electrocardiogram, a Doppler echocardiogram both to evaluate cardiac walls and valves and to measure systolic BP of pulmonary artery, an abdominal ultrasonography, a computed tomography of brain, and a magnetic resonance imaging (MRI) of hips were performed. Other bones for avascular necrosis were scanned according to the patients' complaints. So avascular necrosis of bones was diagnosed by means of MRI (8). Systolic BP of the pulmonary artery of 40 mmHg or higher is accepted as pulmonary hypertension (9). The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% (10). Acute chest syndrome (ACS) is diagnosed clinically with the presence of new infiltrates on chest x-ray film, fever, cough, sputum production, dyspnea, or hypoxia (11). An x-ray film of abdomen in upright position was taken just in patients with abdominal distention or discomfort, vomiting, obstipation, or lack of bowel movement, and ileus is diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity on the abdomen. CRD is diagnosed with a persistent serum creatinine level of 1.3 mg/dL or higher in males and 1.2 mg/dL or higher in females. Cirrhosis is diagnosed with physical examination findings, laboratory parameters, and ultrasonographic evaluation. An exercise electrocardiogram is performed in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken for the exercise electrocardiogram positive cases. So CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as the movement disorders in the cardiac walls. Rheumatic heart disease (RHD) is diagnosed with the echocardiographic findings, too. Stroke is diagnosed by the computed tomography of brain. Eventually, patients with the total plasma bilirubin value of lower than 5.0 mg/dL were collected into the first and 5.0 mg/dL and higher were collected into the second groups, and compared in between. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

We studied 253 patients (128 females) with the total plasma bilirubin value of lower than 5.0 mg/dL and 109 patients (43 females) with the value of 5.0 mg/dL and higher. There were 31 death cases during the ten-year follow up period (14 females with a mean age of 33.3 ± 9.2 (19-47) and 17 males with a mean age of 30.2 ± 8.4 (19-50) years, $p>0.05$). The mean total bilirubin values of the plasma were 2.7 versus 9.7 mg/dL in the first and second groups, $p<0.000$, respectively. The mean ages were similar in the first and second groups (30.2 versus 31.7 years, $p>0.05$, respectively). Interestingly, male ratio was higher in the second group, significantly (60.5% versus 49.4%, $p<0.05$). Similarly, ileus (3.9% versus 10.0%, $p<0.01$), digital clubbing (6.3% versus 26.6%, $p<0.001$), leg ulcers (12.2% versus 20.1%, $p<0.05$), pulmonary hypertension (9.4% versus 23.8%, $p<0.001$), cirrhosis (1.5% versus 15.5%, $p<0.001$), CRD (6.7% versus 12.8%, $p<0.05$), and exitus (4.7% versus 11.9%, $p<0.001$) were all higher in patients with a plasma bilirubin value of 5.0 mg/dL and higher, significantly. Although the transfused units of RBC in their lives (45.7 versus 37.1 units), CHD (22.0% versus 16.6%), COPD (22.9% versus 16.2%), RHD (10.0% versus 6.3%), AVN (28.4% versus 24.5%), disseminated teeth losses (3.6% versus

2.7%), and ACS (5.5% versus 3.1%) were also higher in patients with the total plasma bilirubin value of 5.0 mg/dL and higher, the differences were nonsignificant (p>0.05 for all) probably due to the small sample size of these patients (Table 1).

Discussion

SCD are chronic inflammatory processes on vascular endothelium terminating with accelerated atherosclerosis induced end-organ failures in early years of life (12, 13). Hemoglobin S (HbS) causes loss of elastic and biconcave disc shaped structures of RBC. Probably loss of elasticity instead of shape is the main pathology since sickling is rare in peripheric blood samples of the SCD patients with associated thalassemia minor, and human survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during whole lifespan, but exaggerated with inflammations, infections, and various stresses of the body. The hard RBC induced chronic endothelial damage, inflammation, edema, and fibrosis terminate with disseminated tissue hypoxia all over the body (14, 15). As a difference from other causes of chronic endothelial damage, the SCD may keep vascular endothelium particularly at the capillary level (16), since the capillary system is the main distributor of the hard cells into the tissues. The hard cells induced chronic endothelial damage builds up an advanced atherosclerosis in much younger ages of the patients. As a result, mean lifespans of the patients were 48 and 42 years in females and males in the literature, respectively (17), whereas they were 33.3 and 30.2 years in the present study. The great differences may be secondary to delayed diagnosis, delayed initiation of hydroxyurea therapy, and inadequate RBC supports during emergencies in Turkey (18). Actually, RBC supports must be given immediately during all medical or surgical events in which there is evidence of clinical deterioration in the SCD (11). RBC supports decrease sickle cell concentration in circulation and suppress bone marrow for the production of abnormal RBC. So it decreases sickling-induced endothelial damage and inflammation all over the body.

Digital clubbing is characterized by increased normal angle of 165° between nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (19). The exact cause and significance is unknown but chronic tissue hypoxia is highly suspected (20). In the previous study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (7). But according to our experiences, digital clubbing is frequently associated with smoking and pulmonary, cardiac, and hepatic disorders which are characterized with chronic tissue hypoxia (3). As an explanation for this hypothesis, lungs, heart, and liver are closely related organs and their functions are affected in a short period of time. On the other hand, digital clubbing is also common in patients with the SCD and its prevalence was 12.4% in the present study. It probably shows chronic tissue

Table 1: Characteristic features of the study patients

Variables	Cases with a total bilirubin value of less than 5.0 mg/dL	*p*-value	Cases with a total bilirubin value of 5.0 mg/dL and higher
Number	253		109
Mean age (year)	30.2±10.0 (5-59)	Ns*	31.7 ± 9.4 (15-58)
Male ratio	*49.4%*	*<0.05*	*60.5%*
BMI† (kg/m²)	21.7 ± 3.2 (14.3-32.5)	Ns	21.3 ± 3.5 (14.5-35.8)
Transfused RBC‡ units	37.1 ± 47.5 (0-339)	Ns	45.7 ± 63.7 (0-434)
Total bilirubin (mg/dL)	*2.7 ± 1.0 (0.6-4.9)*	*0.000*	*9.7 ± 7.3 (5-55.2)*
Ileus	*3.9%*	*<0.01*	*10.0%*
Digital clubbing	*6.3%*	*<0.001*	*26.6%*
Leg ulcers	*12.2%*	*<0.05*	*20.1%*
Pulmonary hypertension	*9.4%*	*<0.001*	*23.8%*
Cirrhosis	*1.5%*	*<0.001*	*15.5%*
CRD§	*6.7%*	*<0.05*	*12.8%*
CHD¶	16.6%	Ns	22.0%
COPD**	16.2%	Ns	22.9%
RHD***	6.3%	Ns	10.0%
AVN****	24.5%	Ns	28.4%
Stroke	11.8%	Ns	11.0%
Disseminated teeth losses (< 20 teeth present)	2.7%	Ns	3.6%
ACS*****	3.1%	Ns	5.5%
Exitus	*4.7%*	*<0.001*	*11.9%*

*Nonsignificant (p>0.05) †Body mass index ‡Red blood cells §Chronic renal disease ¶Coronary heart disease **Chronic obstructive pulmonary disease ***Rheumatic heart disease ****Avascular necrosis of bone *****Acute chest syndrome

hypoxia caused by disseminated endothelial damage, inflammation, and edema at the capillary level in the SCD. Beside the effects of SCD, the higher prevalences of smoking, COPD, and clubbing in males ($p<0.001$ for all) may also show some additional roles of smoking, COPD, and male sex on digital clubbing (21).

Leg ulcers are seen in 10 to 20% of patients with the SCD (20), and the ratio was 14.6% in the present study. Its incidence increases with age, male sex, and HbSS genotype (22). Similarly, its ratio was higher in males (19.8% versus 7.0%, $p<0.001$), and mean age of the patients with leg ulcers was significantly higher than the others (35.3 versus 29.8 years, $p<0.000$) in the above study (21). The leg ulcers have an intractable nature, and around 97% of healed ulcers relapse in a period of one year (22). As evidence of their atherosclerotic nature, the leg ulcers occur in distal areas with less collateral blood flow in the body (22). The hard RBC induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillary level may be the major cause in the SCD (23). Prolonged exposure to the hard bodies due to the pooling of blood in the lower extremities may also explain the leg but not arm ulcers in the SCD. The hard RBC induced venous insufficiencies may also accelerate the process by pooling of causative hard bodies in the legs, and vice versa. Pooling of blood in the lower extremities may also have some effects on development of venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis. Pooling of blood in the lower extremities may also have some effects on the delayed wound and fracture healings in the lower extremities. Beside the hard RBC, smoking and alcohol may also have some additional effects on the leg ulcers since both of them are more common in males. Hydroxyurea is the first drug that was approved by the Food and Drug Administration for the treatment of SCD (16). It is an oral, cheap, safe, and effective drug that blocks cell division by suppressing formation of deoxyribonucleotides which are the building blocks of DNA (18). Its main action may be suppression of hyperproliferative white blood cells (WBC) and platelets (PLT) in the SCD (24). Although presence of continuous damage of hard RBC on endothelium, severity of the destructive process is probably exaggerated by the patients' own immune systems. Similarly, lower WBC counts were associated with lower crises rates, and if a tissue infarct occurs, lower WBC counts may decrease severity of pain and tissue damage (25). According to our 15-year experience on the SCD, prolonged resolution of leg ulcers with hydroxyurea may also suggest that the leg ulcers may be secondary to increased WBC and PLT counts induced prolonged endothelial damage, inflammation, and edema at the capillary level in the SCD.

Varices are abnormally dilated veins with tortuous courses, and they usually occur in the lower extremities. Related factors include pregnancy, obesity, menopause, aging, and heredity. In other words, varices are more common in females and metabolic syndrome. Normally, leg muscles pump veins to return blood against gravity, and the veins have pairs of leaflets of valves to prevent blood from flowing backwards. When the leaflets are damaged, varices and/or telangiectasias develop. Deep vein thrombosis (DVT) may also cause varicose veins. Varicose veins are the most common in superficial veins of the legs, which are subject to higher pressure when standing up, thus patient's physical examination should be performed in upright position. Although the relatively younger mean ages of the patients in the above study (30.8 and 30.3 years in males and females, respectively) (21) and significantly lower BMI of the SCD cases in the literature (15), DVT and/or varices and/or telangiectasias of the lower limbs were higher among the study cases (9.0% versus 6.6% in males and females, respectively, $p>0.05$) indicating an additional venous endothelial involvement in the SCD (21).

Both frequency and complications of cirrhosis are increasing in the world. For example, it was the 10th leading cause of death for men and the 12th for women in the United States in 2001 (4). Although the improvements of health services worldwide, the increased morbidity and mortality of cirrhosis may be explained by aging of the human being and increased prevalence of excess weight all over the world. For example, nonalcoholic fatty liver disease (NAFLD) affects up to one third of the world population, and it has become the most common cause of chronic liver disease even in children and adolescents at the moment (26, 27). NAFLD is a marker of pathological fat deposition combined with a low-grade chronic inflammation, which results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerotic process (26). Besides terminating with cirrhosis, NAFLD is associated with higher overall mortality rates as well as with increased prevalence of cardiovascular diseases (27). Authors reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased mean carotid artery intima-media thickness (CIMT) (27, 28). NAFLD and cirrhosis may be considered as the hepatic consequences of the metabolic syndrome (29). Probably smoking also plays a role in the endothelial inflammatory process of the liver, since the systemic inflammatory effects of smoking on endothelial cells is well-known with Buerger's disease and COPD (30). Increased oxidative stresses, inactivation of antiproteases, and release of proinflammatory mediators may terminate with a systemic atherosclerosis in smokers. The atherosclerotic effects of alcohol is much more prominent in hepatic endothelium probably due to the highest concentrations of its metabolites in the liver. Similarly, aging alone may be another cause of systemic atherosclerosis that prevents adequate tissue oxygenation. Chronic infectious and inflammatory processes may also terminate with an accelerated atherosclerosis all over the body (31). For example, chronic hepatitis C virus infection raised CIMT, and normalisation of hepatic function with viral clearance may be secondary to reversal of favourable lipids observed with the chronic infection (31). As a result, beside COPD, ileus, leg ulcers, digital clubbing, CHD, CRD, and stroke, cirrhosis may also be one of the several consequences of the metabolic syndrome and SCD. The higher total bilirubin values of the plasma may show the severity of hemolytic process initiated at birth and/or an advanced hepatic disease in the present study.

Both frequency and complications of CRD are increasing all over the world, again. For instance, 1.9 to 2.3 millions of people have CRD in Canada (32). The Centers for Disease Control and Prevention in the USA found that CRD affected an estimated

16.8% of adults above the age of 20 years between 1999 and 2004 (33). Similarly, the increased frequency and complications of CRD may be explained by aging of the societies and increased prevalence of excess weight all over the world, since CRD may also be one of the terminal endpoints of the metabolic syndrome, and an eventual advanced atherosclerosis may be the underlying cause of the CRD (34). Aging, sedentary lifestyle, physical inactivity, excess weight, smoking, alcohol, inflammatory and infectious processes, cancers, and SCD may be some triggering causes of the endothelial inflammation in the kidneys. The inflammatory process is enhanced by release of various chemical factors by lymphocytes to repair the damaged renal tissues, especially endothelial cells of the renal arterioles. Due to the continuous irritation of the endothelial cells in the above pathologies, prominent changes develop in the architecture of the renal tissues with advanced atherosclerosis, fibrosis, and tissue hypoxia and infarcts. Excess weight induced metabolic abnormalities such as hyperglycemia, dyslipidemia, elevated BP, and insulin resistance cause various cellular stresses which accelerate tissue inflammation and immune cell activation further (35). For example, age ($p= 0.04$), high-sensitivity C-reactive protein ($p= 0.01$), mean arterial BP ($p= 0.003$), and DM ($p= 0.02$) had significant correlations with CIMT (34). Increased renal tubular sodium reabsorption, impaired pressure natriuresis, volume expansion due to the activation of sympathetic nervous system and renin-angiotensin system, and physical compression of kidneys by visceral fat tissue may be some mechanisms of the increased BP with excess weight (36). Excess weight also causes renal vasodilation and glomerular hyperfiltration which initially serve as compensatory mechanisms to maintain sodium balance due to the increased tubular reabsorption (36). However, along with the increased BP, these changes cause a hemodynamic burden on the kidneys in the long term that causes chronic endothelial damage (37). With prolonged weight excess, there are increased urinary protein excretion, lost nephron function, and exacerbated HT. With the development of dyslipidemia and DM in the overweight and obese individuals, CRD progresses much more rapidly (36). On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the etiology of CRD (38). The inflammatory and eventual atherosclerotic effects of smoking are much more prominent in the respiratory endothelium due to the highest concentrations of its metabolites there. Although some authors reported that alcohol was not related with the CRD (38), it is not logical since various metabolites of alcohol circulate even in the blood vessels of the kidneys and give harm to the vascular endothelium, there. Similarly, aging alone may be another cause of the CRD by means of the systemic atherosclerotic effects. Chronic inflammatory or infectious processes may also terminate with the accelerated atherosclerosis on the renal endothelium (31). Although CRD is mainly an advanced atherosclerotic process of the renal vasculature, there are close relationships between CRD and other consequences of the metabolic syndrome including CHD, COPD, PAD, cirrhosis, and stroke (39). For example, the most common cause of death in the CRD is cardiovascular diseases rather than the renal failure again (40). In another definition, CRD may actually be one of the several consequences of the metabolic syndrome and SCD, again.

COPD is the third leading cause of death with various causes in the world (41). It is an inflammatory disease that mainly affects the pulmonary vasculature. Aging, smoking, and excess weight may be the major underlying causes. As also observed in the study, alcohol may also be an important cause in the inflammatory process (42). For example, COPD was one of the most common diagnoses in patients with alcohol dependence (43). Furthermore, 30-day readmission rates were higher in the COPD patients with alcoholism (44). Probably an accelerated atherosclerotic process is the main structural background of functional changes, characteristics of the COPD. The inflammatory process of vascular endothelium is enhanced by release of various chemicals by inflammatory cells, and it terminates with an advanced fibrosis, atherosclerosis, and pulmonary losses. Although the COPD may mainly be an accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of associated endothelial inflammation all over the body (45, 46). For instance, there may be close relationships between COPD, CHD, PAD, and stroke (47). Furthermore, two-thirds of mortality cases were caused by cardiovascular diseases and lung cancers in the COPD, and the CHD was the most common cause in a multi-center study of 5.887 smokers (48). When the hospitalizations were researched, the most common causes were the cardiovascular diseases again (48). In another study, 27% of all mortality cases were due to the cardiovascular diseases in the moderate and severe COPD patients (49). Similarly, COPD may also be one of the terminal endpoints of the SCD due to the higher prevalence of COPD associated with priapism, leg ulcers, clubbing, CHD, CRD, and stroke (50).

Probably pulmonary hypertension is also found among the atherosclerotic endpoints of the SCD. It is defined as the increased BP in pulmonary artery, vein, or capillaries. It is seen in 60% of systemic sclerosis, 40% of SCD, 14% of systemic lupus erythematosus, 21% of rheumatoid arthritis, 5% of portal hypertension, and 0.5% of human immunodeficiency virus infected patients (51). Whereas we detected pulmonary hypertension just in 12.2% of the SCD patients in the above study (42). Younger mean ages of the study cases (30.6 ± 9.8 years) may be the main cause of the lower prevalence (42). Pulmonary hypertension and COPD may actually have similar atherosclerotic underlying mechanisms during the development but pulmonary hypertension may be a more advanced disease since its mean age is higher (34.0 versus 33.6 years), prevalence is lower (12.2% versus 16.3%), and it is nearly equally seen in both genders compared to COPD (52.8% versus 78.8% in males) (42). On the other hand, venous pulmonary hypertension is the most common type in society (52). In venous pulmonary hypertension, the left heart fails to pump blood efficiently, leading to pooling of blood in the lungs. This causes pulmonary edema and pleural effusions. In chronic thromboembolic pulmonary hypertension, blood vessels are blocked or narrowed with clots, which leads to a similar pathophysiology with arterial pulmonary hypertension (53). In hypoxic pulmonary hypertension, hypoxia is thought to cause vasoconstriction or tightening of pulmonary arteries. This pathophysiology may also be the major underlying mechanism in the SCD due to the inflammated and edematous capillary endothelium, secondary to the damage of abnormally hardened RBC in the lungs (54).

Whatever the initial cause, pulmonary hypertension involves vasoconstriction and tightening of blood vessels connected to and within lungs. This further increases BP within lungs and impairs their blood flow. Eventually, increased workload of heart causes thickening and enlargement of right ventricle, right heart failure, and cor pulmonale. As blood flowing through lungs decreases, left heart receives less blood. This blood may also carry less oxygen than normal as in the SCD due to the capillary endothelial inflammation and edema. Thus it becomes harder and harder for the left heart to pump sufficient oxygen to the rest of body, particularly during physical activities. Although various arterial and venous involvement mechanisms, capillary endothelial involvement may be the major underlying cause of pulmonary hypertension in the SCD since the capillary system is the main distributor of the abnormally hardened RBC into the lungs.

As a conclusion, SCD are severe inflammatory processes on vascular endothelium, particularly at the capillary level and terminate with accelerated atherosclerosis induced end-organ failures in early years of life. Total bilirubin value of the plasma may have prognostic significance due to the higher prevalence of ileus, digital clubbing, leg ulcers, pulmonary hypertension, cirrhosis, CRD, and exitus in patients with the plasma bilirubin value of 5.0 mg/dL and higher. The higher bilirubin values may either show the severity of hemolytic process initiated at birth or an advanced hepatic involvement in such cases.

References

1. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2005; 365(9468): 1415-1428.

2. Helvaci MR, Kaya H, Sevinc A, Camci C. Body weight and white coat hypertension. Pak J Med Sci 2009; 25(6): 916-921.

3. Helvaci MR, Aydin LY, Aydin Y. Digital clubbing may be an indicator of systemic atherosclerosis even at microvascular level. HealthMED 2012; 6(12): 3977-3981.

4. Anderson RN, Smith BL. Deaths: leading causes for 2001. Natl Vital Stat Rep 2003; 52(9): 1-85.

5. 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): 3143-3421.

6. Vandemergel X, Renneboog B. Prevalence, aetiologies and significance of clubbing in a department of general internal medicine. Eur J Intern Med 2008; 19(5): 325-329.

7. Schamroth L. Personal experience. S Afr Med J 1976; 50(9): 297-300.

8. 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): 274-283.

9. 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): 615-621.

10. 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): 347-365.

11. Davies SC, Luce PJ, Win AA, Riordan JF, Brozovic M. Acute chest syndrome in sickle-cell disease. Lancet 1984; 1(8367): 36-38.

12. Helvaci MR, Yaprak M, Abyad A, Pocock L. Atherosclerotic background of hepatosteatosis in sickle cell diseases. World Family Med 2018; 16(3): 12-18.

13. Helvaci MR, Davarci M, Inci M, Yaprak M, Abyad A, Pocock L. Chronic endothelial inflammation and priapism in sickle cell diseases. World Family Med 2018; 16(4): 6-11.

14. 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): 11442-11448.

15. Helvaci MR, Kaya H. Effect of sickle cell diseases on height and weight. Pak J Med Sci 2011; 27(2): 361-364.

16. 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): 1033-1048.

17. 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): 1639-1644.

18. Helvaci MR, Aydin Y, Ayyildiz O. Hydroxyurea may prolong survival of sickle cell patients by decreasing frequency of painful crises. HealthMED 2013; 7(8): 2327-2332.

19. Myers KA, Farquhar DR. The rational clinical examination. Does this patient have clubbing? JAMA 2001; 286(3): 341-347.

20. Toovey OT, Eisenhauer HJ. A new hypothesis on the mechanism of digital clubbing secondary to pulmonary pathologies. Med Hypotheses 2010; 75(6): 511-513.

21. Helvaci MR, Tekin B, Abyad A, Pocock L. Alarming consequences of the sickle cell diseases. World Family Med 2018; 16(7): 14-21.

22. Trent JT, Kirsner RS. Leg ulcers in sickle cell disease. Adv Skin Wound Care 2004: 17(8); 410-416.

23. Minniti CP, Eckman J, Sebastiani P, Steinberg MH, Ballas SK. Leg ulcers in sickle cell disease. Am J Hematol 2010; 85(10): 831-833.

24. 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.

25. Charache S. Mechanism of action of hydroxyurea in the management of sickle cell anemia in adults. Semin Hematol 1997; 34(3): 15-21.

26. Bhatia LS, Curzen NP, Calder PC, Byrne CD. Non-alcoholic fatty liver disease: a new and important cardiovascular risk factor? Eur Heart J 2012; 33(10): 1190-1200.

27. Pacifico L, Nobili V, Anania C, Verdecchia P, Chiesa C. Pediatric nonalcoholic fatty liver disease, metabolic syndrome and cardiovascular risk. World J Gastroenterol 2011; 17(26): 3082-3091.

28. Mawatari S, Uto H, Tsubouchi H. Chronic liver disease and arteriosclerosis. Nihon Rinsho 2011; 69(1): 153-157.

29. Bugianesi E, Moscatiello S, Ciaravella MF, Marchesini G. Insulin resistance in nonalcoholic fatty liver disease. Curr Pharm Des 2010; 16(17): 1941-1951.

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): 376-379.

31. Mostafa A, Mohamed MK, Saeed M, Hasan A, Fontanet A, Godsland I, et al. Hepatitis C infection and clearance: impact on atherosclerosis and cardiometabolic risk factors. Gut 2010; 59(8): 1135-1140.

32. Levin A, Hemmelgarn B, Culleton B, Tobe S, McFarlane P, Ruzicka M, et al. Guidelines for the management of chronic kidney disease. CMAJ 2008; 179(11): 1154-1162.

33. Centers for Disease Control and Prevention (CDC). Prevalence of chronic kidney disease and associated risk factors--United States, 1999-2004. MMWR Morb Mortal Wkly Rep 2007; 56(8): 161-165.

34. 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): 203-208.

35. 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): 2933-2943.

36. 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.

37. 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): 242-246.

38. 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): 479-487.

39. Bonora E, Targher G. Increased risk of cardiovascular disease and chronic kidney disease in NAFLD. Nat Rev Gastroenterol Hepatol 2012; 9(7): 372-381.

40. 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): 2034-2047.

41. Rennard SI, Drummond MB. Early chronic obstructive pulmonary disease: definition, assessment, and prevention. Lancet 2015; 385(9979): 1778-1788.

42. Helvaci MR, Arslanoglu Z, Celikel A, Abyad A, Pocock L. Pathophysiology of pulmonary hypertension in sickle cell diseases. Middle East J Intern Med 2018; 11(2): 14-21.

43. 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): 459-468.

44. 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): 905-915.

45. 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): 1477-1482.

46. 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): 627-643.

47. 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): 2653-2658.

48. 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): 333-339.

49. 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): 411-415.

50. Helvaci MR, Erden ES, Aydin LY. Atherosclerotic background of chronic obstructive pulmonary disease in sickle cell patients. HealthMED 2013; 7(2): 484-488.

51. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2009; 54(1): 43-54.

52. Duffels MG, Engelfriet PM, Berger RM, van Loon RL, Hoendermis E, Vriend JW, et al. Pulmonary arterial hypertension in congenital heart disease: an epidemiologic perspective from a Dutch registry. Int J Cardiol 2007; 120(2): 198-204.

53. Oudiz RJ. Classification of pulmonary hypertension. Cardiol Clin 2016; 34(3): 359-361.

54. Gladwin MT, Sachdev V, Jison ML, Shizukuda Y, Plehn JF, Minter K, et al. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. N Engl J Med 2004; 350(9): 886-895.

Triglycerides may be acute phase reactants which are not negatively affected by pathologic weight loss

Mehmet Rami Helvaci (1)
Atilla Yalcin (1)
Orhan Ekrem Muftuoglu (1)
Abdulrazak Abyad (2)
Lesley Pocock (3)

(1) Specialist of Internal Medicine, MD
(2) Middle-East Academy for Medicine of Aging, MD
(3) medi+WORLD International

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

Received September 2020. Accepted October 2020. Published December 1, 2020.
Please cite this article as: Mehmet Rami Helvaci et al. Triglycerides may be acute phase reactants which are not negatively affected by pathologic weight loss. Middle East J Intern Med 2020; 13(3): 14-19. DOI: 10.5742/MEJIM2020.93793

ABSTRACT

Background: Sickle cell diseases (SCD) are chronic inflammatory process on vascular endothelium terminating with atherosclerosis induced end-organ failures in early decades of life.

Methods: Consecutive patients with the SCD and controls were studied.

Results: The study included 363 patients with the SCD (169 females) and 255 age and gender-matched controls (119 females). Mean ages of the SCD patients were similar in males and females (31.1 versus 31.0 years, respectively, p>0.05). Although the body weight and body mass index (BMI) were significantly retarded in the SCD patients (59.9 versus 71.5 kg and 21.9 versus 25.6 kg/m2, respectively, p= 0.000 for both), the body heights were similar in both groups (164.9 versus 167.0 cm, p>0.05). Parallel to the retarded body weight, fasting plasma glucose (92.8 versus 97.6 mg/dL, p= 0.005), total cholesterol (121.4 versus 165.0 mg/dL, p= 0.000), low density lipoproteins (70.4 versus 102.4 mg/dL, p= 0.000), high density lipoproteins (26.0 versus 39.6 mg/dL, p= 0.000), systolic blood pressures (BP) (115.2 versus 122.6 |mmHg, p= 0.000), and diastolic BP (73.0 versus 86.6 mmHg, p= 0.000) were all lower in the SCD patients, significantly. Interestingly, only the triglycerides (TG) value was higher in the SCD patients (129.4 versus 117.3 mg/dL, p= 0.000), significantly. Similarly, the alanine aminotransferase value was not suppressed in the SCD patients, too (27.4 versus 27.3 U/L, respectively, p>0.05).

Conclusion: Plasma TG may be acute phase reactants indicating disseminated endothelial injury and accelerated atherosclerosis all over the body, and their plasma values are not negatively affected by pathologic weight loss.

Key words: Sickle cell diseases, chronic endotelial damage, atherosclerosis, triglycerides, acute phase reactants, metabolic syndrome, body weight

Introduction

Chronic endothelial damage may be the major underlying cause of aging and death by causing end-organ insufficiencies in human beings (1, 2). Much higher blood pressures (BP) of the afferent vasculature may be the major accelerating factor by causing recurrent injuries on vascular endothelial cells. Probably, whole afferent vasculature including capillaries are mainly involved in the process. Thus the term of venosclerosis is not as famous as atherosclerosis in the medical literature. Due to the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic nature, and eventually reduce blood supply to the terminal organs, and increase systolic BP further. Some of the well-known accelerating factors or indicators of the inflammatory process are physical inactivity, sedentary lifestyle, animal-rich diet, smoking, alcohol, overweight, hypertriglyceridemia, dyslipidemia, impaired fasting glucose, impaired glucose tolerance, white coat hypertension, chronic inflammations, prolonged infections, and cancers for the development of terminal consequences including obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), chronic renal disease (CRD), mesenteric ischemia, osteoporosis, stroke, dementia, other end-organ insufficiencies, aging, and death (3, 4). Although early withdrawal of the accelerating factors can delay terminal consequences, after development of HT, DM, cirrhosis, COPD, CRD, CHD, PAD, mesenteric ischemia, osteoporosis, stroke, dementia, other end-organ insufficiencies, and aging, endothelial changes cannot be reversed completely due to their fibrotic nature. The accelerating factors and terminal consequences are researched under the titles of metabolic syndrome, aging syndrome, or accelerated endothelial damage syndrome in the medical literature, extensively (5, 6). Although their normal limits have not been determined clearly yet, high plasma triglycerides (TG) values may be significant indicators of the metabolic syndrome (7). Due to the significant association between high plasma TG values and CHD, Adult Treatment Panel (ATP) III adopts lower cutpoints for TG abnormalities than did ATP II (8, 9). Although ATP II determined the normal upper limit of TG as 200 mg/dL in 1994, World Health Organisation in 1999 (10) and ATP III in 2001 reduced the normal upper limit as 150 mg/dL (9). Although these cutpoints are usually used to define borders of the metabolic syndrome, there are suspicions about the safest upper limit of the TG in the plasma. On the other hand, sickle cell diseases (SCD) are chronic inflammatory process on vascular endothelium terminating with accelerated atherosclerosis induced end-organ failures and a shortened survival in both genders (11, 12). Hemoglobin S (Hb S) causes loss of elastic and biconcave disc shaped structures of red blood cells (RBC). Probably loss of elasticity instead of shape is the major problem since sickling is rare in peripheric blood samples of the patients with associated thalassemia minors, and human survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during whole lifespan, but exaggerated with inflammations, infections, and various stresses of the body. The hard RBC induced chronic endothelial damage, inflammation, and fibrosis terminate with disseminated tissue hypoxia in the whole body (13, 14). As a difference from other causes of chronic endothelial damage, the SCD may keep vascular endothelium particularly at the capillary level (15), since the capillary system is the main distributor of the hard cells into the tissues. The hard RBC induced chronic endothelial damage builds up an advanced atherosclerosis in early decades of life. Vascular narrowings and occlusions induced tissue ischemia and infarctions are the final consequences of the SCD, so the mean life expectancy is decreased by 25 to 30 years in the SCD (16).

Material and Methods

The study was performed in the Medical Faculty of the Mustafa Kemal University on consecutive patients with the SCD and routine check up cases between March 2007 and June 2016. The SCD are diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography. Medical histories of the SCD patients were learnt. A complete physical examination was performed by the same internist. Body mass index (BMI) of each case was calculated by the measurements of the same internist instead of by verbal expressions. Weight in kilograms is divided by height in meter squared (9). Systolic and diastolic BP were checked after a 5-minute rest in seated position using the mercury sphygmomanometer (ERKA, Germany), and no smoking was permitted during the previous 2 hours. Cases with acute painful crisis or any other inflammatory event were treated at first, and the laboratory tests and clinical measurements were performed on the silent phase. Check up procedures including fasting plasma glucose (FPG), total cholesterol (TC), high density lipoproteins (HDL), TG, serum creatinine, alanine aminotransferase (ALT), markers of hepatitis viruses A, B, C and human immunodeficiency virus, a posterior-anterior chest x-ray film, and an electrocardiogram were performed. Eventually, the mean body weight, height, BMI, FPG, TC, low density lipoproteins (LDL), HDL, TG, ALT, and systolic and diastolic BP were detected in each group, and compared in between. Mann-Whitney U Test, Independent-Samples t Test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 363 patients with the SCD (169 females) and 255 control cases (119 females). Mean ages of the SCD patients were similar in males and females (31.1 versus 31.0 years, respectively, $p>0.05$). Although the mean body weight and BMI were retarded in the SCD patients, significantly (59.9 versus 71.5 kg and 21.9 versus 25.6 kg/m2, respectively, $p= 0.000$ for both), the mean body heights were similar in both groups (164.9 versus 167.0 cm, $p>0.05$). Parallel to the retarded mean body weight, FPG (92.8 versus 97.6 mg/dL, $p= 0.005$), TC (121.4 versus 165.0 mg/dL, $p= 0.000$), LDL (70.4 versus 102.4 mg/dL, $p= 0.000$), HDL (26.0 versus 39.6 mg/dL, $p= 0.000$), systolic BP (115.2 versus 122.6 mmHg, $p= 0.000$), and diastolic BP (73.0 versus 86.6 mmHg, $p= 0.000$) were all lower in the SCD patients, significantly. Interestingly, only the mean TG value was higher in the SCD patients (129.4 versus 117.3 mg/dL, $p= 0.000$), significantly. Similarly, the mean ALT value was not suppressed in the SCD patients, too (27.4 versus 27.3 U/L, respectively, $p>0.05$) (Table 1).

Table 1: Characteristic features of the study cases

Variables	Patients with SCD*	*p*-value	Control cases
Number	363		255
Mean age (year)	31.0 ±9.2 (17-59)	Ns†	31.2 ±8.6 (16-45)
Female ratio	46.5% (169)	Ns	46.6% (119)
Weight (kg)	59.9 ± 11.8 (30-122)	0.000	71.5 ± 16.4 (40-128)
Height (cm)	164.9 ±9.1 (142-194)	Ns	167.0 ±8.6 (147-192)
BMI‡ (kg/m^2)	21.9 ± 3.6 (14.3-46.4)	0.000	25.6 ± 5.8 (15.8-53.5)
FPG§ (mg/dL)	92.8 ± 12.5 (57-125)	0.005	97.6 ± 19.7 (66-269)
TC‖ (mg/dL)	121.4 ± 32.2 (65-296)	0.000	165.0 ± 54.3 (72-510)
LDL¶ (mg/dL)	70.4 ± 28.4 (20-270)	0.000	102.4 ± 41.1 (29-313)
HDL** (mg/dL)	26.0 ± 9.4 (4-60)	0.000	39.6 ± 13.2 (7-95)
*TG*** (mg/dL)*	*129.4 ± 90.4 (31-1216)*	*0.000*	*117.3 ± 107.4 (24-931)*
ALT**** (U/L)	27.4 ±16.2 (4-118)	Ns	27.3 ±21.6 (6-117)
Systolic BP***** (mmHg)	115.2 ± 15.7 (80-190)	0.000	122.6 ± 19.4 (80-200)
Diastolic BP (mmHg)	73.0 ± 12.3 (50-120)	0.000	86.6 ± 13.6 (60-120)

***Sickle cell diseases †Nonsignificant (p>0.05) ‡Body mass index §Fasting plasma glucose ‖Total cholesterol ¶Low density lipoproteins **High density lipoproteins ***Triglycerides ****Alanine aminotransferase *****Blood pressures**

Discussion

SCD can affect all vascular organ systems of the body (17, 18). Aplastic crises, sequestration crises, hemolytic crises, acute chest syndrome, avascular necrosis of the femoral and humeral heads, priapism and infarction of the penis, osteomyelitis, acute papillary necrosis of the kidneys, CRD, occlusions of retinal arteries and blindness, pulmonary HT, bone marrow necrosis induced dactilitis in children, chronic punched-out ulcers around ankles, hemiplegia, and cranial nerve palsies are only some of the several presentation types of the SCD. Eventually, the median ages of death were 42 years in males and 48 years in females in the literature (16). Delayed diagnosis, delayed initiation of hydroxyurea therapy, and inadequate RBC supports during emergencies may decrease the expected survival time in the SCD patients further (19). Actually, RBC supports must be given immediately during all medical or surgical procedures in which there is evidence of clinical deterioration in the SCD (20). RBC supports decrease sickle cell concentration in the circulation and suppress bone marrow for the production of abnormal RBC. So it decreases sickling induced endothelial damage and inflammation all over the body. Due to the great variety of clinical presentation types, it is not surprising to see that the mean body weight and BMI were significantly retarded in patients with the SCD in the present study. On the other hand, as an opposite finding to some other reports (21, 22), the body heights were similar in patients with the SCD and control cases, here. Probably due to the significantly lower mean body weight and BMI, mean values of the FPG, TC, LDL, HDL, systolic BP, and diastolic BP were also lower in patients with the SCD, which can be explained by definition of the metabolic syndrome (23, 24).

Cholesterol, TG, and phospholipids are the major lipids of the body. Cholesterol is an essential structural component of animal cell membrane, bile acids, adrenal and gonadal steroid hormones, and vitamin D. TG are fatty acid esters of glycerol, and they are the major lipids transported in the blood. The bulk of fat tissue deposited all over the body is in the form of TG. Phospholipids are TG that are covalently bound to a phosphate group. Phospholipids regulate membrane permeability, remove cholesterol from the body, provide signal transmission across the membranes, act as detergents, and help in solubilization of cholesterol. Cholesterol, TG, and phospholipids do not circulate freely in the plasma instead they are bound to proteins, and transported as lipoproteins. There are five major classes of lipoproteins including chylomicrons, very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), LDL, and HDL in the plasma. Chylomicrons carry exogenous TG from intestine to liver via the thoracic duct. VLDL are produced in the liver, and carry endogenous TG from the liver to the peripheral organs. In the capillaries of adipose and muscle tissues, 90% of TG is removed by a specific group of lipases. So VLDL are converted into IDL by removal of TG. Then IDL are degraded into LDL by removal of more TG. So VLDL are the main sources of LDL in the plasma. LDL deliver cholesterol from the liver to other parts of the body. Although the liver removes the majority of LDL from the circulation, a small amount is uptaken by scavenger receptors on macrophages which may migrate into arterial walls and become the foam cells of atherosclerotic plaques. HDL remove fats and cholesterol from cells, including within arterial wall atheroma, and carry the cholesterol back to the liver and steroidogenic organs including adrenals, ovaries, and testes for excretion, reutilization, and disposal. All of the carrier lipoproteins in the plasma are under dynamic control, and are readily affected by diet, illness, drug, body weight, and BMI. Thus lipid analysis should be performed during a steady state. But the metabolic

syndrome alone is a low-grade inflammatory process on vascular endothelial cells all over the body. Thus the metabolic syndrome alone may be a cause of the abnormal lipoproteins levels in the plasma. On the other hand, although HDL are commonly called 'the good cholesterol' due to their roles in removing excess cholesterol from the blood, and protecting the arterial walls against atherosclerosis (25), recent studies did not show similar results, and low plasma HDL levels may alert clinicians about searching for additional metabolic or inflammatory pathologies in the body (26, 27). Normally, HDL may show various anti-atherogenic properties including reverse cholesterol transport and anti-oxidative and anti-inflammatory properties (27). However, HDL may become 'dysfunctional' in pathological conditions which means that relative compositions of lipids and proteins, as well as the enzymatic activities of HDL are altered (26). For instance, properties of HDL are compromised in patients with DM due to the oxidative modification and glycation as well as the transformation of HDL proteomes into proinflammatory proteins. Additionally, the highly effective agents of increasing HDL levels such as niacin, fibrates, and cholesteryl ester transfer protein inhibitors did not reduce all cause mortality, CHD mortality, myocardial infarction, or stroke (28). While higher HDL levels are correlated with cardiovascular health, medications used to increase HDL did not improve the health (28). In other words, while high HDL levels may correlate with better cardiovascular health, specifically increasing one's HDL values may not increase cardiovascular health (28). So they may just be some indicators instead of being the main actors of the process. Beside that, HDL particles that bear apolipoprotein C3 are associated with increased risk of CHD (29). Similarly, BMI, FPG, DM, and CHD were the lowest between the HDL values of 40 and 46 mg/dL, and the prevalence of DM was only 3.1% between these values against 22.2% of outside of these limits (30). In another definition, the moderate HDL values may also be the results instead of the causes of the better health parameters.

Probably excess weight may be the most common cause of vasculitis, worldwide, and the leading cause of major health problems in this century. It leads to structural and functional abnormalities in many organ systems of the body (31). Adipose tissue produces leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines, all of which behave as acute phase reactants in the plasma (32). Excess weight induced chronic low-grade vascular endothelial inflammation may play a significant role in the pathophysiology of disseminated atherosclerosis in whole body (1, 2). On the other hand, excess weight may cause an increased blood volume as well as an increased cardiac output thought to be the result of an increased oxygen need of the excessive fat tissue. The prolonged increase in the blood volume may lead to myocardial hypertrophy, terminating with a decreased cardiac compliance. Similar to the present study, FPG and TC values increased parallel to the increased BMI values (33). Combination of these cardiovascular risk factors will eventually terminate with an increased left ventricular stroke work and higher risks of arrhythmias, cardiac failure, and sudden death. Additionally, the prevalence of CHD and stroke increased parallel to the increased BMI values in another study (34), and risk of death from all causes including cancers increased throughout the range of moderate to severe excess weight in all age groups (35). The relationships between excess weight, increased BP, and higher plasma TG values were described in the metabolic syndrome, extensively (36), and clinical manifestations of the syndrome include obesity, hypertriglyceridemia, hyperbetalipoproteinemia, HT, insulin resistance, and proinflammatory and prothrombotic states (36). Similarly, prevalence of smoking (42.2% versus 28.4%, $p<0.01$), excess weight (83.6% versus 70.6%, $p<0.01$), DM (16.3% versus 10.3%, $p<0.05$), and HT (23.2% versus 11.2%, $p<0.001$) were all higher in the hypertriglyceridemia group in another study (37). On the other hand, the prevalence of hyperbetalipoproteinemia was similar both in the hypertriglyceridemia (200 mg/dL and higher) and control groups (18.9% versus 16.3%, $p>0.05$, respectively) in the above study (37). Similarly, plasma LDL values increased just up to the plasma TG value of 200 mg/dL but no more in another study (38). Beside that, the mean BMI values increased just up to the plasma TG value of 150 mg/dL, significantly ($p<0.05$ for each step) (38). On the other hand, the greatest number of deteriorations in the metabolic parameters were observed just above the plasma TG value of 60 mg/dL (38). In our opinion, although excess weight does not affect each individual with the same severity, overweight, obesity, severe obesity, and morbid obesity histories of years should be added into the calendar age with various degrees during calculation of physiological age of the individuals.

Although the obvious consequences of excess weight on health, nearly three-quarters of cases above the age of 30 years have excess weight (39). The prevalence of excess weight increases by decades, particularly after the third decade, up to the eighth decade of life (39). So 30th and 70th years of age may be the breaking points of life for body weight, and aging may be the major determining factor of excess weight. Relatively decreased physical and mental stresses after the age of 30 years, and debility and comorbid disorders induced restrictions after the age of 70 years may be the major causes for the changes of BMI at these ages. Interestingly, the mean age and BMI increased just up to the plasma TG values of 200 mg/dL and 150 mg/dL in the above study, respectively (38). So smoking remained as the major underlying factor for the hypertriglyceridemia above the plasma TG value of 200 mg/dL. Beside that, the mean BMI values were 24.6, 27.1, 29.4, 29.9, and 30.0 kg/m2 in the five study groups, respectively (38). In other words, only cases with the plasma TG values lower than 60 mg/dL had a normal mean BMI value (38). On the other hand, the mean age and TG value of the first group were 35.6 years and 51.0 mg/dL, respectively (38). They were 43.6 years and 78.3 mg/dL in the second, 47.7 years and 122.2 mg/dL in the third, and 51.2 years and 174.1 mg/dL in the fourth groups, respectively (38). In another definition, TG values increased about 7.8 mg/dL for each year of aging up to 200 mg/dL in the plasma (38). So aging alone may be another risk factor for chronic low-grade inflammation on vascular endothelium all over the body.

Although ATP III reduced the normal upper limit of plasma TG as 150 mg/dL in 2001 (9), whether or not much lower limits provide some additional benefits for human body remains unclear (40). Similar to the recent study (41), prevalence of smoking was the highest in the highest TG having group in the above study (38) which may also indicate the inflammatory role of smoking on vascular endothelium in the metabolic syndrome,

since TG may behave as acute phase reactants in the plasma. BMI, FPG, HT, DM, COPD, and CRD increased parallel to the increased plasma TG values from the first up to the fifth groups, continuously in the above study (38). In out opinion significantly increased mean age by the increased plasma TG values may be secondary to aging induced decreased physical and mental stresses, which eventually terminate with excess weight and its consequences. Interestingly, although the mean age increased from the lowest TG having group up to TG value of 200 mg/dL, then it decreased (38). The similar trend was also seen with the mean LDL values (38). These trends may be due to the fact that although the borderline high TG values (150-199 mg/dL) are seen together with physical inactivity and overweight, the high TG (200-499 mg/dL) and very high TG values (500 mg/dL or higher) may be secondary to genetic factors, smoking, and terminal consequences of the metabolic syndrome including obesity, DM, HT, COPD, cirrhosis, CRD, PAD, CHD, and stroke (9). But although the underlying causes of the high and very high plasma TG values may be a little bit different, probably risks of the terminal endpoints of the metabolic syndrome do not change in them. For example, prevalence of HT, DM, and COPD were the highest in the highest TG having group in the above study (38). Eventually, although some authors reported that lipid assessment can be simplified by measurements of TC (42), the present study and most of the others indicated a causal relationship between higher TG values and irreversible end-points of the metabolic syndrome (43).

As a conclusion, plasma TG may be acute phase reactants indicating disseminated endothelial injury and accelerated atherosclerosis all over the body, and their plasma values are not negatively affected by pathologic weight loss.

References

1. Widlansky ME, Gokce N, Keaney JF Jr, Vita JA. The clinical implications of endothelial dysfunction. J Am Coll Cardiol 2003; 42(7): 1149–1160.

2. Helvaci MR, Seyhanli M. What a high prevalence of white coat hypertension in society! Intern Med 2006; 45(10): 671-674.

3. Helvaci MR, Kaya H, Seyhanli M, Yalcin A. White coat hypertension in definition of metabolic syndrome. Int Heart J 2008; 49(4): 449-457.

4. Helvaci MR, Sevinc A, Camci C, Yalcin A. Treatment of white coat hypertension with metformin. Int Heart J 2008; 49(6): 671-679.

5. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2005; 365(9468): 1415-1428.

6. Franklin SS, Barboza MG, Pio JR, Wong ND. Blood pressure categories, hypertensive subtypes, and the metabolic syndrome. J Hypertens 2006; 24(10): 2009-2016.

7. Helvaci MR, Kaya H, Gundogdu M. Association of increased triglyceride levels in metabolic syndrome with coronary artery disease. Pak J Med Sci 2010; 26(3): 667-672.

8. National Cholesterol Education Program. Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). Circulation 1994; 89(3): 1333-1445.

9. 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): 3143-3421.

10. World Health Organization. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Report of a WHO consultation 1999.

11. Helvaci MR, Yaprak M, Abyad A, Pocock L. Atherosclerotic background of hepatosteatosis in sickle cell diseases. World Family Med 2018; 16(3): 12-18.

12. Helvaci MR, Davarci M, Inci M, Yaprak M, Abyad A, Pocock L. Chronic endothelial inflammation and priapism in sickle cell diseases. World Family Med 2018; 16(4): 6-11.

13. 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): 11442-11448.

14. Helvaci MR, Kaya H. Effect of sickle cell diseases on height and weight. Pak J Med Sci 2011; 27(2): 361-364.

15. 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): 1033-1048.

16. 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): 1639-1644.

17. Hutchinson RM, Merrick MV, White JM. Fat embolism in sickle cell disease. J Clin Pathol 1973; 26(8): 620-622.

18. Helvaci MR, Davran R, Abyad A, Pocock L. What a high prevalence of rheumatic heart disease in sickle cell patients. World Family Med 2020; 18(9): 80-85.

19. Helvaci MR, Aydin Y, Ayyildiz O. Hydroxyurea may prolong survival of sickle cell patients by decreasing frequency of painful crises. HealthMED 2013; 7(8): 2327-2332.

20. Davies SC, Luce PJ, Win AA, Riordan JF, Brozovic M. Acute chest syndrome in sickle-cell disease. Lancet 1984; 1(8367): 36-38.

21. Al-Saqladi AW, Cipolotti R, Fijnvandraat K, Brabin BJ. Growth and nutritional status of children with homozygous sickle cell disease. Ann Trop Paediatr 2008; 28(3): 165-189.

22. Zemel BS, Kawchak DA, Ohene-Frempong K, Schall JI, Stallings VA. Effects of delayed pubertal development, nutritional status, and disease severity on longitudinal patterns of growth failure in children with sickle cell disease. Pediatr Res 2007; 61(5 Pt 1): 607-613.

23. Helvaci MR, Kaya H, Sevinc A, Camci C. Body weight and white coat hypertension. Pak J Med Sci 2009; 25(6): 916-921.

24. Helvaci MR, Abyad A, Pocock L. High and low density lipoproteins may be negative acute phase proteins of the metabolic syndrome. Middle East J Nursing 2020; 14(1): 10-16.

25. Toth PP. Cardiology patient page. The "good cholesterol": high-density lipoprotein. Circulation 2005; 111(5): 89-91.

26. Femlak M, Gluba-Brzózka A, Cialkowska-Rysz A, Rysz J. The role and function of HDL in patients with diabetes mellitus and the related cardiovascular risk. Lipids Health Dis 2017; 16(1): 207.

27. Ertek S. High-density lipoprotein (HDL) dysfunction and the future of HDL. Curr Vasc Pharmacol 2018; 16(5): 490-498.

28. Keene D, Price C, Shun-Shin MJ, Francis DP. Effect on cardiovascular risk of high density lipoprotein targeted drug treatments niacin, fibrates, and CETP inhibitors: meta-analysis of randomised controlled trials including 117,411 patients. BMJ 2014; 349: 4379.

29. Sacks FM, Zheng C, Cohn JS. Complexities of plasma apolipoprotein C-III metabolism. J Lipid Res 2011; 52(6): 1067-1070.

30. Helvaci MR, Abyad A, Pocock L. What a low prevalence of diabetes mellitus between the most desired values of high density lipoproteins in the plasma. World Family Med 2020; 18(7): 25-31.

31. Funahashi T, Nakamura T, Shimomura I, Maeda K, Kuriyama H, Takahashi M, et al. Role of adipocytokines on the pathogenesis of atherosclerosis in visceral obesity. Intern Med 1999; 38(2): 202–206.

32. Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? Arterioscler Thromb Vasc Biol 1999; 19(4): 972–978.

33. 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): 147–156.

34. 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): 245–252.

35. 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): 1097–1105.

36. Tonkin AM. The metabolic syndrome(s)? Curr Atheroscler Rep 2004; 6(3): 165-166.

37. Helvaci MR, Aydin LY, Maden E, Aydin Y. What is the relationship between hypertriglyceridemia and smoking? Middle East J Age and Ageing 2011; 8(6).

38. Helvaci MR, Abyad A, Pocock L. The safest upper limit of triglycerides in the plasma. World Family Med 2020; 18(1): 16-22.

39. Helvacı MR, Kaya H, Ozer C. Aging may be the major determiner factor of excess weight. Middle East J Age and Ageing 2008; 5(2).

40. Helvaci MR, Tonyali O, Abyad A, Pocock L. The safest value of plasma triglycerides. World Family Med 2019; 17(7): 22-27.

41. Helvaci MR, Tonyali O, Abyad A, Pocock L. Smoking may be a cause of hypertriglyceridemia. World Family Med 2019; 17(8): 14-18.

42. Di Angelantonia E, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, et al. Major lipids, apolipoproteins, and risk of vascular disease. JAMA 2009; 302(18): 1993-2000.

43. Sarwar N, Sandhu MS, Ricketts SL, Butterworth AS, Di Angelantonia E, Boekholdt SM, et al. Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies. Lancet 2010; 375(9726): 1634-1639.

Parkinson's Disease: An update on Pathophysiology, Epidemiology, Diagnosis and Management Part 5: Management Strategies

Abdulrazak Abyad

CEO, Abyad Medical Center, Lebanon.
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

Correspondence:
Dr. Abdulrazak Abyad
Email: aabyad@cyberia.net.lb

Received September 2020. Accepted October 2020. Published December 1, 2020.
Please cite this article as: Abdulrazak Abyad.. Parkinson's Disease: An update on Pathophysiology, Epidemiology, Diagnosis and Management . Part 5: Management Strategies. Middle East J Intern Med 2020; 13(3): 20-24. DOI: 10.5742/MEJIM2020.93795

ABSTRACT

Parkinson's disease has a wide variety of motor and non-motor symptoms. Treatment aims to control the patient's symptoms by replenishing the dopaminergic system with levodopa or dopamine agonists. Monoamine oxidase B inhibitors are also effective first-line drugs. Keeping symptoms under continual control early in the course of the disease may have beneficial effects as Parkinson's disease progresses. Therapy is tailored to each patient's response to the drugs and their ability to tolerate them. Limited responses of motor and many non- motor symptoms may require the addition of other treatments. The adverse effects of drugs used in the treatment of Parkinson's disease are usually reversible. As the disease progresses and problems accumulate, deep brain stimulation (DBS) surgery may be a reasonable therapeutic option for some individuals, although many people with PD do not qualify for DBS for a variety of reasons. In addition nonpharmacological alternatives are helpful , including diet, exercise and occupational therapy. However, the majority of people with PD can lead full and active lives with good symptom control for many years.

Key words: Parkinson's Disease, Pathophysiology, Epidemiology, Diagnosis, Management

Introduction

It is crucial for individuals with PD to understand that while the underlying condition progresses steadily, the clinical course differs greatly with each person over several years. A competent and caring healthcare professional, can assist the person with PD and his or her care partner with careful management of PD symptoms to establish a treatment plan consisting of suitable drugs, daily exercise, a balanced diet, social involvement and cognitive exercises, and other therapies.

Parkinson's disease treatment is intended to maximize the quality of life of the patient. Just one of the many services available is addiction treatment. To better deal with the diverse needs of patients and their families, the necessary role of other allied health professionals must be stressed. There will also be a significant effect on the participation of nurses, social workers and occupational, physiotherapy and speech therapy facilities. Various medical treatments, as well as other options from a multidisciplinary, would be needed to assist patients coping with their illness at various levels of impairment. The ultimate aim of medical management is to allow the patient to work as near as possible to normal without suffering therapy side effects. The signs are not a concern in many cases of early illness and medication is unnecessary. Table 1 lists the types of medications that are used.

Treatment should be personalized to the individual's needs, as always. Patients should be encouraged to make informed treatment decisions and strive to include the caregivers as much as the patient requires.

Management strategies

When Parkinson's disease is diagnosed, whether to initiate any type of drug therapy and which medications to use are the most important questions to determine. This will rely in part, on the degree of functioning and extent of impairment of the patient. Planning for long-term development and impairment often includes early treatment of Parkinson's disease. How will the potential complications of a chronic, degenerative condition that will have to be treated over a period of several years be avoided or delayed?

The main method of treating symptoms of Parkinson's disease is treatment with antiparkinsonian medications. The right therapeutic choices may lead the patient to additional years of productive work and may even decrease the period of later dependent living. However, among the available choices, no single medication is suitable for initial therapy for all patients.

The choice of treatments, in addition to clinical considerations, is conditioned by the financial resources of the individual patient. The older demographic differs markedly in terms of access to prescription payments. In most larger populations, services that can be used nationally and locally for the management and education of patients with PD are readily accessible. Because a decade of medical management may be necessary, the primary care physician should pay special attention to the patient's personality, concerns, desires, and aspirations about PD therapy. Ideally, any therapy decisions may include those patients early on. Others will prefer to avoid medical attention longer than others will, and some will require gentle encouragement to try any drug. There is no evidence that indicates that withholding therapy actually eliminates potential side effects.

There is no universal consensus as to how and when to begin antiparkinsonian-drug treatment. No two individuals with Parkinson's have the same symptoms, so it's a case of trial and error at first. But no drug treatment for Parkinson's is really successful until the correct formula is identified for the symptoms.

In Parkinson's disease, dopaminergic drugs are the foundation of symptomatic care for motor symptoms. Levodopa was the first symptomatic therapy for Parkinson's disease, discovered in the 1960s, followed by the availability of dopamine agonists and inhibitors of monoamine oxidase B. The decision as to which care to initiate has, until recently, been not fully discussed. There is no single drug currently prescribed for initiation of treatment, but consideration should be given to factors such as symptom intensity, embarrassment, willingness to perform tasks, cost and patient preference. The patient may prefer not to begin therapy if the symptoms are very mild (1, 2).

Since levodopa-induced irregular movements (dyskinesia) are more likely to occur in patients with early onset disease, dopamine agonists are often introduced as initial treatment, but this early benefit of dopamine agonists over levodopa declines with time (about 10 years) (1). There is also some questionable proof of neuroprotection with the 1 mg daily dose of monoamine oxidase B inhibitor rasagiline; (3) but it is expensive and may not be covered by insurance.

Levodopa is frequently initiated first because of the increased risk of neuropsychiatric adverse effects from dopamine agonists in late-onset Parkinson's disease (1). Levodopa is much better at managing Parkinson's motor symptoms than dopamine agonists and monoamine oxidase B inhibitors, but after long-term usage or high-dose therapy, dyskinesia and motor fluctuations occur (4). With the addition of adjunctive procedures, the patient will possibly require multiple prescription changes over time (5,6). Most patients taking dopamine agonists will also need levodopa after two to five years (7).

Since Parkinson-plus syndromes (e.g. multiple system atrophy and progressive supranu-clear paralysis) respond to levodopa at an early stage, this drug should be tested for at least several months at doses of up to 1000 mg/d before non-responsiveness is concluded (8). After a trial with levodopa, the condition should also be re-evaluated. In about 80% of patients with idiopathic Parkinson's disease, levodopa responsiveness occurs (8). While bradykinesia and rigidity respond well to levodopa, tremor is not seen to have this consistent response (9).

In patients with early-onset Parkinson disease and extreme tremor, anticholinergic medications, such as trihexyphenidyl, can be used, but not as a first option due to reduced effectiveness and potential for neuropsychiatric adverse effects (2). Recent data suggest that injections of botulinum toxin can effectively treat Parkinson's disease tremors (10).

In 5 percent of Parkinson's disease patients and up to 20 percent of those taking dopamine agonists, behavioral addictions and impulse control disorders occur (11, 12). Risk factors for impulse control disorders include younger age (perhaps linked to the prescribing activity of dopamine agonists in this group), personality seeking novelty, family history of addiction, dopamine agonist use, and previous history of impulse control disorders (11).

Dopamine dysregulation syndrome is a form of addictive behavior that occurs in up to 4% of patients and is characterized by the compulsive overuse of dopaminergic drugs, usually short-acting (e.g., levodopa and apomorphine), which affect physical, social and occupational functioning (12). Punding involves repeated, often meaningless, stereotyped actions, such as sorting or disassembly, which occurs in up to 15% of Parkinson's disease patients (13). Dopamine dysregulation syndrome and punding can occur with the use of short-acting dopaminergic agents, including levodopa (1). Impulse control disord

ers can occur at any time after initiating dopamine agonists.

To prevent acute akinesia or neuroleptic malignant syndrome, antiparkinsonian pharmaceutical products should not be suddenly removed. Owing to the risk of dopamine agonist withdrawal syndrome, dopamine agonists should not be stopped quickly (occurs in 15% of patients taking dopamine agonists; the risk is higher in people with impulse control disorders) (14-16).

Drugs that should be avoided

Drugs that block dopamine receptors in patients with Parkinson's disease can lead to Parkinson's disease or greatly exacerbate motor symptoms which can lead to malignant neuroleptic syndrome. These include neuroleptics such as haloperidol, thioridazine, chlorpromazine, promethazine, fluphenazine, risperidone and olanzapine; antiemetics such as metoclopramide and prochlorperidone; tetrabenazine; and antihypertensives such as methyldopa (17,18). For those receiving monoamine oxidase B inhibitors, meperidine should be avoided (19).

Drugs to avoid

These are some (but not all) of the drugs to avoid in Parkinson's:

- chlorpromazine (Largactil)
- fluphenazine (Modecate)
- fluphenazine with nortriptyline (Motival)
- perphenazine (Fentazin/Triptafen)
- trifluoperazine (Stelazine)
- flupenthixol (Fluanxol/Depixol)
- haloperidol (Serenace/Haldol)
- metoclopramide (Maxalon)
- prochlorperazine (Stemetil)
- Decongestants or cold remedies

Managing motor and nonmotor symptoms in advanced disease

Most patients respond well to levodopa; however, motor fluctuations and dyskinesias will grow in 40 percent-50 percent of patients within five years of chronic levodopa treatment and in 70 percent-80 percent after 10 years of treatment (1, 20,21). Motor fluctuations are spontaneous changes in motor response to dopaminergic therapy that may be erratic, whereas dyskinesias are involuntary and intrusive movements resulting from levodopa, primarily choreiform (22). In patients receiving less than 400–500 mg per day of levodopa, dyskinesias are less likely to develop (23). In patients with early-onset disease and possibly in women (6,20,23,24), there is a higher cumulative frequency of dyskinesias, wearing off and on-off changes in symptoms. Dyskinesias may suggest better medication response, and most patients tend to be "on" rather than "off" with dyskinesia. (24)

In one study, 20 percent of Parkinson's disease patients had problematic motor fluctuations and 4 percent had five-year dyskinesias, which were serious enough to warrant a change in care (25). In order to minimize 'off' period, catechol O-methyltransferase (COMT) inhibitors, such as entacapone, administered with each levodopa-carbidopa tablet; monoamine oxidase B inhibitors, such as rasagiline or selegiline; and dopamine agonists, such as pramipexole, ropinirole, rotigotine patch and bromocriptine (2), may be offered. Owing to the dangers of pulmonary and cardiac valve fibrosis, ergot derivatives such as bromocriptin should be used with caution. To minimize motor variability, modified-release levodopa preparations, such as controlled-release preparations, can be used but should not be used as a first option. The use of combined formulations of levodopa-carbidopa with COMT inhibitors has been shown to be associated with earlier onset and increased dyskinesia frequency (26). Dyskinesias can be known to be minimized by amantadine, an antiviral with antiglutamatergic effects; it is effective in 60%-70% of patients (27). Axial signs appear to develop later in the disorder, including postural dysfunction and gait, and can be less receptive to dopaminergic therapies. There is evidence that cholinesterase inhibitors and/or methylphenidate are being investigated (28).

Table 1: Drug used to treat Parkinson's disease					
Drug or drug class	Mechanism of action	Side effects	Specific drugs	Typical daily therapeutic dose range	Typical dose frequency
Anticholinergics	Block acetylcholine receptors	Dry mouth, dry eyes, urinary retention, exacerbation of glaucoma and cognitive impairment	Trihexyphenidyl Benztropine Ethoprpazine	1-6 mg 1-6 mg 25-100 mg	Tid Tid Tid
Amantadine	Blocks NMDA receptors and acetylcholine receptors and promotes release of dopamine	Cognitive dysfunction, peripheral edema and skin rash	Amantadine	50-200 mg, but caution is required with dose escalation in elderly patients or patients with renal insufficiency	Bid
L-dopa	Metabolism o dopamine in cells that contain dopa-decarboxylase	Nausea, hypotension, hallucinations and psychosis, dystonic and chroreiform dyskinesias	L-dopa/carbidopa, L-dopa/benseracide, Sinemet CR	100-2000 mg/d as condition advances. Sinemet CR has about 25% reduced biovailability	From tid to every 2 h
Dopamine agonists	Directly stimulate dopamine receptors	Nausea, hypotension, hallucinations and psychosis, pulmonary fibrosis (for ergots), sudden onset of sleep	Bromocriptine Pergolide Ropinirole Pramipexole	15-30 mg 1.5-5.0 mg 6.0-24 mg 1.5-5.0 mg	3-4 times/d Tid Tid Tid
Monoamine oxidase (MAO) inhibitors	Block MAO-B receptors to reduce dopamine metabolism	Nausea, dizziness, sleep disorder and impaired cognition	Selegiline	5-10 mg	Bid
Catechol O-methyltransferase (COMT) inhibitors	Block peripheral COMT activity to improve L-dopa pharmacokinetics	L-dopa-related side-effect exacerbation, diarrhea, urine discoloration	Entacapone	200 mg with each dose of L-dopa up to 1600 mg/d	With each dose of L-dopa