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REVIEW

Overview of dyslipidemia and metabolic syndrome in myeloproliferative neoplasms

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Abstract

Myeloproliferative neoplasms (MPNs) occur due to the abnormal proliferation of one or more terminal myeloid cell lines in peripheral blood. Subjects suffering from MPNs display a high burden of cardiovascular risk factors, and thrombotic events are often the cause of death in this population of patients. Herein, we provide a brief overview of dyslipidemia and metabolic syndrome and their epidemiology in MPNs and examine the common molecular mechanisms between dyslipidemia, metabolic syndrome, and MPNs, with a special focus on cardiovascular risk, atherosclerosis, and thrombotic events. Furthermore, we investigate the impact of dyslipidemia and metabolic syndrome on the occurrence and survival of thrombosis in MPN patients, as well as the management of dyslipidemia in MPNs, and the impact of MPN treatment on serum lipid concentrations, particularly as side/adverse effects reported in the context of clinical trials.

Key Words: Polycythemia vera; Essential thrombocythemia; Myelofibrosis; Cardiovascular disease; Hypercholesterolemia; Hypertriglyceridemia; Obesity; Diabetes; Inflammation; Oxidative stress

Core Tip: The topic of dyslipidemia in myeloproliferative neoplasms (MPNs) has only been superficially studied to date. Although it is well known that cardiovascular risk factors impact the management of MPNs and increase the risk of thrombosis which is the main cause of death in MPNs, most investigations have overlooked dyslipidemia as a significant contributor to thrombotic risk and to the risk of death in MPNs. Herein, we provide, to the best of our knowledge, the first overview of lipid abnormalities in MPNs.

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INTRODUCTION

Hematopoietic pluripotent stem cells (HPSCs) exhibit a remarkable capacity for self-renewal and undergo differentiation into myeloid or lymphoid lineages. This intricate hematopoietic process culminates in the emergence of various mature blood cells (BCs), which include red BCs (RBCs), lymphocytes, granulocytes, megakaryocytes, and macrophages. The orchestration of hematopoiesis is intricately governed by the complex interplay of the bone marrow microenvironment, growth factors, and transcriptional regulators[1].

Myeloproliferative neoplasms (MPNs) occur due to the abnormal proliferation of one or more terminal myeloid cell lines in peripheral blood. This results in the manifestation of a heterogeneous group of disorders. The initial term "myeloproliferative disorders," originally introduced by William Dameshek in 1951, has been formally standardized and rephrased as "myeloproliferative neoplasms" by the World Health Organization in 2016[2].

Within the classification of MPNs, the updated document encompasses seven distinct subcategories: chronic myeloid leukemia, chronic neutrophilic leukemia, polycythemia vera (PV), primary myelofibrosis (PMF), essential thrombocythemia (ET), chronic eosinophilic leukemia-not otherwise specified and MPN, unclassifiable. Notably, it is imperative to highlight that mastocytosis no longer falls under the MPN category. This revised categorization represents a pivotal advance in the field, indicating a comprehensive and rigorous approach to classifying these complex disorders[2,3].

PV is a chronic myeloproliferative neoplastic disorder characterized by the uncontrolled production of RBCs, resulting in an elevated mass of RBCs. This condition often leads to concurrent stimulation of myeloid and megakaryocytic lineages, leading to increased production of white BCs and platelets. Pathophysiology involves abnormal hematopoietic cell clones with increased sensitivity to growth factors. Signs and symptoms such as headache, dizziness, claudication, and thrombosis arise due to increased blood viscosity. Subjects diagnosed with PV exhibit driver mutations in the Janus kinase 2 (*JAK2*) gene. In > 95% of cases, the *JAK2V617F* mutation is detected in exon 14 of the aforementioned gene, and

the remaining 3%-4% of affected individuals exhibit mutations in exon 12 of the *JAK2* gene[4,5]. Cytogenetic studies reveal abnormal karyotypes in about 34% of patients. PV affects all ethnic groups, with a higher incidence in men, and is usually diagnosed around 60-years-old[6]. In the United States, the overall incidence of PV between 2002 and 2016 was 1.57 (1.55-1.60) per 100000 person years, with fewer cases reported in Japan compared to the United States and Europe[6,7].

ET is another classical BCR-ABL1-negative MPN. It is characterized by excessive platelet production and megakaryocytic hyperplasia in the bone marrow. Initially identified in 1934 under the name "hemorrhagic thrombocythemia", it was subsequently classified as MPN by Damesheck in 1951[8]. About 55% of patients with ET harbor the *JAK2V617F* point mutation[9,10]. ET is related to the development of vascular complications, for example, thrombosis and hemorrhage, which are associated with the presence of thrombocytosis, and there is a possibility of progression of the disease to secondary myelofibrosis (MF)[11,12]. ET is more prevalent among MPNs, affecting 1.0 to 2.5 individuals per 100000 yearly, with a higher incidence in females. The condition becomes more common with age, and most cases present between the ages of 50 and 60[13,14].

PMF is characterized by the clonal overproduction of myeloid cells originating from HPSCs. Although not always present, PMF often involves mutations in the *JAK2*, calreticulin, or myeloproliferative leukemia genes. Additional features include the abnormal presence of collagen fibrosis in the bone marrow, the dysregulated expression of inflammatory cytokines, anemia, hepatosplenomegaly, extramedullary hematopoiesis, constitutional symptoms, cachexia, the risk of progression to acute leukemia, and reduced life expectancy. The incidence of MF in the European Union varies between 0.3 and 1.9 per 100000 people, with an average of 1.1 per 100000[15]. In the United States, the annual incidence of MF is 1.33 per 100000[16]. In high-income countries of the European Union, the prevalence of MF ranges from 0.5 to 9 per 100000 per year[15]. The global prevalence of MF is approximately 1 per 100000 people[16].

BRIEF OVERVIEW OF CARDIOVASCULAR RISK FACTORS IN MPNs

Subjects suffering from MPNs exhibit a high burden of cardiovascular risk factors (CVRFs), thrombotic events often being the cause of death in this patient population[17-19]. In a recent publication by Seguro *et al*[20], the authors conducted a retrospective analysis of hemorrhagic and thrombotic events in a cohort of 334 Brazilian patients with Philadelphia-negative chronic MPNs. The study identified risk factors associated with thrombosis in these patients. The authors of the study used the revised International Prognostic Score in ET to classify patients into four risk categories using four variables: CVRFs, history of thrombosis, age > 60 years, and presence of the *JAK2V617F* mutation. However, CVRFs were not taken into account in the risk assessment of PV and MF in this study. Currently, thrombotic risk in PV is assessed using traditional classification, which classifies individuals as low- or high-risk based on their age (< or > 60 years) and history of thrombosis[20]. In the case of MF, there is currently no validated score to assess thrombotic risk. However, current evidence suggests that one or more CVRF, such as hypertension, diabetes, cigarette smoking, dyslipidemia, or obesity, may increase the risk of thrombosis in MPNs[21]. The previously agreed thrombotic risk classification models for PV and ET introduced an intermediate risk category in addition to the traditional high and low risk categories. This intermediate-risk category included patients under the age of 60 years of age with no history of thrombosis, but with the presence of CVRFs. However, this thrombotic risk classification model is not widely used in clinical practice[22].

Cerquozzi *et al*[23] conducted a study to investigate the association between CVRF and the onset of arterial or venous thrombotic complications in patients with MPNs at or after diagnosis[23]. The findings of their investigation revealed that dyslipidemia, age < 60 years, diabetes, normal karyotype, and hypertension were associated with the development of arterial events. On the other hand, female sex, a history of major hemorrhage, palpable splenomegaly, and age < 60 years were associated with thrombosis in the venous territories[23].

In a recent report by Barbui *et al*[24], hypertension in low-risk patients with PV was emphasized to increase the risk of arterial thrombosis[24]. Currently, for patients with PV or ET who are > 60 years of age and have one or more CVRF, cytoreductive therapy is not recommended. In the revised 2018 management recommendations for classical MPNs negative for BCR-ABL1 issued by European LeukemiaNet, Barbui *et al*[25] argued for the consideration of general risk factors for thrombosis, such as smoking consumption, diabetes mellitus, hypertension and hypercholesterolemia, in the management of MPNs[25].

Accurso *et al*[26] analyzed a cohort of 603 MPN patients who were followed from January 1997 to December 2019 to assess the frequency of CVRF in this population of patients[26]. They investigated the prevalence of smoking, hypertension, diabetes, dyslipidemia, and obesity in different disease subgroups, including 138 cases of overt PMF or post-ET/post-PV MF, 48 cases of prefibrotic PMF, 169 cases of PV, and 249 cases of ET. They also differentiated patients with a single CVRF from those with multiple CVRFs. The overall prevalence of CVRFs in the MPN cohort was 75.95%, with 40.63% of patients having only one CVRF and 35.32% having multiple risk factors. The median age of CVRF patients was 67.57 years, while those without CVRF had a median age of 53.98 years ($P < 0.001$). The high frequency of CVRF in MPNs raises important questions regarding prognosis and therapeutic decisions[26]. However, conclusive data on the impact of CVRFs on thrombotic risk in Philadelphia-negative chronic MPNs are lacking. Prospective studies are needed to determine the risk of thrombotic inflammation in patients with MPNs, both with and without CVRF. If it is demonstrated that CVRFs significantly increase thrombotic risk in MPNs, cytoreductive therapy may be warranted for these individuals. More research is needed to establish the exact relationship between cardiovascular and thrombotic risk in MPNs and inform appropriate therapeutic strategies.

EPIDEMIOLOGY OF DYSLIPIDEMIA IN MPNs AND ITS IMPACT ON THROMBOSIS AND SURVIVAL

Dyslipidemia and metabolic syndrome (MetS) remain some of the most common CVRFs in the general population. Dyslipidemia has traditionally been defined as alterations in serum cholesterol concentrations: total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and/or high-density lipoprotein cholesterol (HDL-C) and/or triglycerides (TGs) [27]. However, recent evidence suggests that secondary lipid biomarkers, for example, lipoprotein(a), apolipoproteins, lipid subclasses, and/or subfractions, may provide additional information in terms of cardiovascular risk assessment[27-29]. Furthermore, the MetS which comprises the association in various levels of insulin resistance, hypertension, atherogenic dyslipidemia, and central obesity is also associated with the appearance of cardiovascular events[30].

The interplay of dyslipidemia, MetS, and obesity has been extensively studied not only in the field of cardiology but also by oncology researchers. Metabolic dysfunction has been particularly associated with the development and outcome of a myriad of solid cancers, as well as hematologic malignancies such as lymphoma, multiple myeloma, acute and chronic leukemias, as well as myelodysplastic syndromes and MPNs[31-33]. Furthermore, low concentrations of apolipoprotein A1 (hazard ratio [HR] = 1.59, 95% confidence interval [CI]: 1.22-2.08; $P < 0.001$] and/or high-density lipoprotein cholesterol (HR = 1.66, 95%CI: 1.22-2.26; $P < 0.001$) have been associated with an elevated risk of MPNs even after multiple comparisons were considered[33].

A recent cohort study that evaluated 1537 individuals diagnosed with *JAK2V617F*-positive MPNs reported that dyslipidemia is the second most common CVRF after hypertension in these disorders. Overall, 14.1% of the cases analyzed suffered from hyperlipidemia, which particularly affected PV (16.1%) and PMF (16%) rather than ET subjects (12%). Furthermore, MPN individuals who developed thrombotic events were more frequently described as dyslipidemia compared to those who were thrombosis-free (62.1% *vs* 37.9%; $P < 0.0001$). However, this investigation confirmed CVRFs as predictive factors of thrombotic complications in MPNs[34].

Similarly, Guglielmelli *et al*[35] highlighted that, in their cohort of 382 subjects with prefibrotic PMF, dyslipidemia (12%) was the third most common CVRF after hypertension (27%) and smoking (14%)[35]. Furthermore, dyslipidemia was the CVRF most frequently discovered (16%) after hypertension (42.2%) and diabetes (18.6%) in a cohort of 668 patients with PMF and MF post-PV/post-ET. Furthermore, the authors revealed a negative association between survival and the presence of dyslipidemia in MF (HR = 4.65, 95%CI: 3.11-6.95; $P < 0.001$) in the univariate analysis. However, multivariate Cox proportional hazard models failed to demonstrate their impact on survival[36]. Accurso *et al*[37] also confirmed that dyslipidemia is second among CVRF in people with PV (28.75%) and ET (24.89%) after hypertension based on data derived from a cohort of 403 MPN patients and that CVRFs are associated with an elevated risk of thrombotic events in MPNs[37]. Furthermore, Stein *et al*[38] highlighted that dyslipidemia was notably associated with a history of thrombotic events (odds ratio [OR] = 2.31, 95%CI: 1.00-5.34; $P = 0.05$) in MPN subjects who harbor the *JAK2V617F* mutation[38]. Another assessment indicated that CVRF (obesity, dyslipidemia, diabetes, hypertension, use of cigarettes) are predictors of thrombotic complications after MPN diagnosis (HR = 4.22, 95%CI: 2.00-8.92; $P < 0.001$)[39].

Horvat *et al*[40] analyzed a cohort of 258 MPN individuals who developed arterial and/or venous thrombosis and revealed that dyslipidemia was associated with the development of the aforementioned vascular events (OR = 3.5, 95%CI: 1.8-6.8; $P < 0.001$). However, dyslipidemia was more likely to be associated with the development of arterial (OR = 4.1, 95%CI: 2.0-8.3; $P < 0.001$) rather than venous (OR = 1.5, 95%CI: 0.5-4.5; $P = 0.330$) thrombotic complications[40]. When researchers analyzed thrombotic events by MPN subtype and site of thrombosis, dyslipidemia was only related to arterial but not venous thrombosis in ET (OR = 4.5, 95%CI: 1.6-12.6; $P = 0.006$) and PMF (OR = 6.1, 95%CI: 1.1-33.6; $P = 0.046$)[40]. Furthermore, a Japanese study indicated that elevated serum TG concentrations are positively associated with thrombotic events in ET (HR = 3.530, 95%CI: 1.630-7.643; $P < 0.001$), whereas elevated serum LDL-C concentrations were marginally associated with vascular events in ET (HR = 2.191, 95%CI: 0.966-4.971; $P = 0.061$) in the univariate model. Furthermore, elevated serum TG concentrations were the only CVRF associated with thrombosis in ET (HR = 3.364, 95%CI: 1.541-7.346; $P = 0.002$) in the multivariate model, while the role of elevated serum LDL-C concentrations warrants further investigation (HR = 2.046, 95%CI: 0.895-4.676; $P = 0.09$). More specifically, serum TG concentrations ≥ 106.19 mg/dL were associated with decreased thrombosis-free survival in patients with ET patients (HR = 2.592; $P = 0.026$)[41].

Košťál *et al*[42] analyzed data from the Czech MPN registry to identify risk factors for stroke and/or transient ischemic attack in anagrelide-treated MPNs, revealing that increased serum TC (34.6% *vs* 28.5%) and TG (30.6% *vs* 19.4%) concentrations were more frequent in MPN patients who developed cerebrovascular events *vs* those who did not. However, in the univariate and multivariate analysis, respectively, only hypertriglyceridemia emerged as a notable risk factor for cerebrovascular events (HR = 1.734, 95%CI: 1.162-2.586; $P = 0.008$) whereas hypercholesterolemia did not impact the onset of these complications. Furthermore, hypertriglyceridemia and not hypercholesterolemia remained a significant risk factor for cerebrovascular events even in MPN individuals who did not receive cytoreductive treatment (OR = 2.265, 95%CI: 1.188-4.318; $P = 0.015$)[42].

It is well established that patients with MPNs experience an elevated occurrence of vascular complications. In the largest epidemiological study on PV, CVRFs such as nonhemorrhagic stroke, congestive heart failure, coronary heart disease, and pulmonary embolism contributed to 41% of all deaths[43]. Nonfatal thrombosis occurred at a rate of 3.8 events per year per 100 persons[44]. Similarly, in patients with ET, the rate of thrombosis ranges from 2% to 4% by patients years. One of these thrombotic complications of particular interest due to its severity is splanchnic vein thrombosis. Other microcirculatory thrombosis can also occur that results in vascular headaches, dizziness, visual impairment, distal paresthesia, and erythromelalgia[43].

Multivariate analyses of CVRFs such as dyslipidemia, hypertension, diabetes, and smoking, which investigated the impact on the occurrence of thrombosis in MPNs, have produced conflicting results. Some authors have reported that these risk factors do not influence vascular complications in MPNs, while others propose that the existence of these risks may elevate a low-risk patient to high-risk ED. In the recent International Prognostic Score of ET thrombosis score, the

CVRFs mentioned above were independent variables influencing the rate of thrombosis[43,44]. However, data from a Japanese ET registry that included 1232 subjects of whom 17.6% exhibited elevated LDL-C and 8.4% elevated TG concentrations, respectively, suggests that dyslipidemia is not a predictor of survival in ET, however, hypertriglyceridemia significantly predicted thrombosis-free survival (HR = 3.018, 95%CI: 1.644-5.540; $P < 0.001$). Elevated LDL-C marginally predicted (HR = 1.722, 95%CI: 0.979-3.029; $P = 0.059$) thrombosis-free survival, which warrants investigating this potential thrombotic risk factor in future assessments[45]. CVRFs also appear to be associated with recurrent thrombosis in ET (OR = 3.148, 95%CI: 1.414-7.010; $P = 0.005$); however, the prevalence of dyslipidemia was similar between patients with/without recurrent thrombotic events[46].

Interestingly, in a multicentric Italian cohort that recruited 816 subjects with PV of whom a number of 44 individuals eventually progressed to secondary MF (post-VV), overweight and/or obese PV patients had reduced chances of developing post-VV MF (HR = 0.38, 95%CI = 0.15-0.94; $P = 0.04$) and, in addition, experienced elevated survival rates (HR = 0.42, 95%CI: 0.18-0.97; $P = 0.04$)[47]. However, it seems that MPN patients who also suffer from obesity show an increased burden of symptoms and a reduced quality of life compared to normal weight MPN subjects[48]. This indicates that the perception of people living with MPNs about their quality of life and total symptom burden is also modeled by their cardiovascular comorbidities and increased symptom scores or reduced quality of life scores are not always indicative of disease progression[48,17]. However, Aswad *et al*[49] reported that obesity does not impact the overall rate of thrombotic events or recurrent thrombosis, nor the rates of arterial/vein thrombosis or microvascular disturbances in MPNs and that hereditary thrombophilia is more likely to contribute to the development of thrombotic complications (OR = 2.26; $P = 0.007$) and in particular arterial thrombosis (OR = 2.04; $P = 0.046$) *vs* CVRF[49].

Table 1 summarizes the most relevant findings regarding the interplay between dyslipidemia and/other metabolic disturbances and thrombosis in MPNs.

MANAGEMENT OF DYSLIPIDEMIA AND METABOLIC SYNDROME IN MPNs AND IMPACT OF MPN THERAPY ON THE LIPID PROFILE

Patients with MPNs often have dyslipidemia and MetS, making their management a clinical challenge that requires a comprehensive and integrated approach. Dyslipidemia, characterized by an abnormal lipid profile, typically involves an increase in TC, LDL-C, and TG levels, along with a decrease in HDL-C levels, respectively. Dyslipidemia can contribute to the development of atherosclerosis and increase the risk of cardiovascular disease, and in patients with MPNs, it can trigger the onset of acute coronary syndromes[50,51].

In patients without MPNs, the treatment of dyslipidemia depends on lifestyle modifications, including diet adjustments, increased physical activity, and weight reduction. Currently, pharmacotherapy, primarily with statins, that is β-Hydroxy β-methylglutaryl-CoA reductase inhibitors, is used when lifestyle modifications are not sufficient. For most patients, the goal is to lower LDL-C levels to less than 100 mg/dL, while those at very high cardiovascular risk may need to target an LDL-C level of less than 70 mg/dL[52]. MetS is a cluster of metabolic conditions: elevated blood pressure, central obesity, elevated serum TG, elevated fasting blood glucose, and low HDL-C levels. Each component independently increases the risk of cardiovascular disease, type 2 diabetes, and all-cause mortality[53]. Treatment of MetS involves primarily targeting its components through lifestyle modifications and pharmacotherapy, as required.

The American Diabetes Association and the American Heart Association have established specific goals for metabolic control in patients with MetS. Targets include blood pressure less than 130/80 mmHg, fasting blood glucose less than 100 mg/dL, and hemoglobin levels A1C below 7.0%. Furthermore, the primary objective of treating dyslipidemia as part of MetS is to reduce LDL-C; however, if TG is 200 mg/dL or greater, a secondary goal is to decrease non-HDL-C by 30% to 50% of the baseline of the patient[54].

In the context of patients with MPNs, these metabolic disorders pose unique challenges. *JAK2* gene mutations, a common feature in MPNs, can exacerbate metabolic dysregulation. These mutations are known to activate the JAK/signal transducer and activator of transcription signaling pathway, leading to the proliferation of hematopoietic cells. JAK2 is an essential component of the insulin receptor signaling pathway; upon binding of insulin to its receptor, JAK2 phosphorylates the insulin receptor, leading to downstream signaling events that facilitate glucose uptake[55]. Some studies have demonstrated that carriers of *JAK2* gene mutations show increased insulin, hypoglycemia, and adipose tissue atrophy, reinforcing the link between this mutation and metabolic disorders[56]. Currently, there is growing evidence that *JAK2* gene mutations can lead to altered lipid metabolism due to increased metabolic demand[57,58].

Furthermore, MPNs are associated with a pro-inflammatory state, which could affect insulin sensitivity and lipid metabolism through key homeostatic factors such as adiponectin, which warrants complete metabolic control[59]. Chronic inflammation is believed to contribute to the development of MetS through various mechanisms, including dysregulated adipocytokine production, increased insulin resistance, and direct effects on lipid metabolism[60,61].

MPN-directed therapies can also influence the metabolic profile of these patients. Ruxolitinib, a JAK1/2 inhibitor, is commonly used in the treatment of MPNs. This drug has been associated with weight gain and metabolic changes. Weight gain associated with ruxolitinib is believed to occur due to blocking leptin signaling in the brain leading to increased fat accumulation[62]. Furthermore, Mesa *et al*[63] detected elevated concentrations of TC and LDL-C in patients treated with ruxolitinib compared to pretreatment levels of TC/LDL-C in the same patient cohort[63]. Ruxolitinib has also been shown to increase systolic blood pressure after 72 wk of administration ($P = 0.03$)[64]. This underscores the need for routine metabolic monitoring and personalized therapeutic strategies in patients with MPNs in such therapies. The use of statins is beneficial in patients with MPNs. In a large population-based cohort study involving 876 patients with ET, Podoltsev *et al*[65] demonstrated improved patient survival using statin therapy[65]. Furthermore, a nationwide

Table 1 Relevant results on the interaction between dyslipidemia and other metabolic disturbances and thrombosis or other factors in myeloproliferative neoplasm

Ref.	Study sample	MPN subtypes	Main findings
Pedersen *et al* [33]	116728	Not specified	↓ Apolipoprotein A1 (HR = 1.59, 95%CI: 1.22-2.08; $P < 0.001$) = ↑ risk of MPNs
Pedersen *et al* [33]	116728	Not specified	↓ HDL-C (HR = 1.66, 95%CI: 1.22-2.26; $P < 0.001$) = ↑ risk of MPNs
Zhang *et al* [34]	1537	PV, ET, PMF	↑ Rates of dyslipidemia in MPNs individuals with thrombotic events *vs* thrombosis-free (62.1% *vs* 37.9%; $P < 0.0001$)
García-Fortes et al[36]	668	PMF, post-PV MF, post-ET MF	Negative association of survival and dyslipidemia in MF (HR = 4.65, 95%CI: 3.11-6.95; $P < 0.001$)
Stein *et al*[38]	164	PV, ET, PMF	Association of dyslipidemia and history of thrombotic events (OR = 2.31, 95%CI: 1.00-5.34; $P = 0.05$) in *JAK2V617F*-positive MPNs
Gu *et al*[39]	567	PV	CVRFs (including dyslipidemia) = predictors of thrombosis after MPN diagnosis (HR = 4.22, 95%CI: 2.00-8.92; $P < 0.001$)
Horvat *et al* [40]	258	PV, ET, PMF	Association between dyslipidemia and vascular events (OR = 3.5, 95%CI: 1.8-6.8; $P < 0.001$), arterial thrombosis (OR = 4.1, 95%CI: 2.0-8.3; $P < 0.001$), venous thrombosis (OR = 1.5, 95%CI: 0.5-4.5; $P = 0.330$), arterial thrombosis in ET (OR = 4.5, 95%CI: 1.6-12.6; $P = 0.006$), and PMF (OR = 6.1, 95%CI: 1.1-33.6; $P = 0.046$)
Furuya *et al* [41]	580	ET	↑ TG positively associated with thrombotic events in ET (HR = 3.530, 95%CI: 1.630-7.643; $P < 0.001$)
Furuya *et al* [41]	580	ET	LDL-C concentrations marginally associated with vascular events in ET (HR = 2.191, 95%CI: 0.966-4.971; $P = 0.061$)
Furuya *et al* [41]	580	ET	↑ TG = only CVRF associated with thrombosis in ET (HR = 3.364, 95%CI: 1.541-7.346; $P = 0.002$)
Furuya *et al* [41]	580	ET	TG ≥ 106.19 mg/dL = ↓ thrombosis-free survival in ET (HR = 2.592; P = 0.026)
Košťál *et al* [42]	1142	PV, ET, PMF	Hypertriglyceridemia not hypercholesterolemia = RF for cerebrovascular events (HR = 1.734, 95%CI: 1.162-2.586; $P = 0.008$)
Košťál *et al* [42]	1142	PV, ET, PMF	Hypertriglyceridemia and not hypercholesterolemia = RF for cerebrovascular events in MPNs without cytoreductive treatment (OR = 2.265, 95%CI: 1.188-4.318; $P = 0.015$)
Hashimoto *et al*[45]	1152	ET	Hypertriglyceridemia predicts thrombosis-free survival (HR = 3.018, 95%CI: 1.644-5.540; $P < 0.001$)
Hashimoto *et al*[45]	1152	ET	↑ LDL-C marginally predicts thrombosis-free survival (HR = 1.722, 95%CI: 0.979-3.029; $P = 0.059$)
Benevolo *et al* [47]	816	PV	overweight/obese PV = ↓ post-PV MF rates (HR = 0.38, 95%CI = 0.15-0.94; $P = 0.04$)
Benevolo *et al* [47]	816	PV	overweight/obese PV = ↑ survival rates (HR = 0.42, 95%CI: 0.18-0.97; $P = 0.04$)
Christensen *et al*[48]	3114	PV, ET, PMF	obesity + MPNs = ↑ symptom burden & ↓ QoL *vs* normal-weight MPNs

CI: Confidence interval; CVRFs: Cardiovascular risk factors; ET: Essential thrombocythemia; HDL-C: High-density lipoprotein cholesterol; HR: Hazard ratio; MF: Myelofibrosis; MPNs: Myeloproliferative neoplasms; OR: Odds ratio; PMF: Primary myelofibrosis; PV: Polycythemia vera; QoL: Quality of life; RF: Risk factor; ↑ increased/elevated; ↓: Reduced/decreased.

Danish case-control study demonstrated lower odds of being diagnosed with MPNs among statin users, alluding to the possible anti-neoplastic mechanisms of statin drugs[66]. The intricate interplay between MPNs, dyslipidemia, and MetS underscores the need for a comprehensive, multipronged approach to patient management. As our understanding of the biological connections between these conditions expands, we can expect to refine our therapeutic strategies further, ultimately improving patient outcomes.

Although the main objective of MPN treatment is to control the overproduction of one or more types of BCs, emerging research has shown that MPN treatments can have unintended impacts on serum lipid concentrations of patients, potentially leading to dyslipidemia and MetS[67]. Dyslipidemia, a condition characterized by an abnormal amount of lipids in the blood, and MetS, a group of conditions including increased blood pressure, high blood sugar, excess body fat around the waist, and abnormal TC or TG levels, have been increasingly reported as side effects of various MPN treatments. These adverse effects can significantly affect the quality of life of patients, and if left untreated, they can contribute to the development of cardiovascular disease, a leading cause of death among patients with MPNs[68]. An

investigation led by Sung *et al*[69] reported that patients treated with ruxolitinib exhibited increased levels of LDL-C and decreased levels of HDL-C, a lipid profile commonly associated with an increased risk of atherosclerotic cardiovascular disease[69]. Interferon-alpha, another treatment prescribed for MPNs, has also been shown to induce changes in lipid profiles. Sun *et al*[70] observed that treatment with pegylated interferon-alpha resulted in lower HDL-C levels in patients with PV, supporting the hypothesis that interferon-alpha may lead to dyslipidemia and therefore increase cardiovascular risk in MPN patients[70].

It is important to note that MPN patients are already at increased risk of thrombosis due to the nature of the disease itself, and the addition of dyslipidemia and MetS can exacerbate this risk. The interplay between MPN treatment, lipid metabolism, and cardiovascular risk is complex and multifaceted. For example, MPN treatments may influence MetS development by inducing weight gain, a common side effect of JAK inhibitors such as ruxolitinib[62]. Furthermore, patients with MPNs often present with inflammation, which can also contribute to dyslipidemia and MetS. Chronic inflammation has been associated with insulin resistance, which is a key driver of MetS. MPN treatments such as ruxolitinib have potent anti-inflammatory effects, but can also affect metabolic homeostasis, leading to adverse metabolic effects[71].

Although these potential side effects are concerning, it is important to note that the benefits of MPN therapy, including control of disease symptoms and improvement in survival, often outweigh these risks. However, these findings highlight the need for regular monitoring of serum lipid profiles and metabolic parameters in patients undergoing MPN treatment. They also emphasize the importance of lifestyle modifications, including diet and physical activity, to counteract these potential side effects. It is crucial that clinicians consider the possible impact of MPN treatments on serum lipid concentrations, dyslipidemia, and MetS. By closely monitoring these parameters, early intervention and educating patients about lifestyle changes, clinicians can help mitigate the risk of cardiovascular disease and improve the overall quality of life for patients with MPNs.

MOLECULAR MECHANISMS COMMON IN DYSLIPIDEMIA, METS AND MPNs

Clonal hematopoiesis is the process of equipotential cloning of hematopoietic stem cells (HSCs) with the aim of providing the body with a sufficient number of HSCs, therefore regulating the amount of its derivatives within the body[72,73]. The process is similar to that of regular cell division. However, since gene replication is prone to errors due to DNA derangement and telomere shortening, the fact that cells with higher potency offer a larger range of expressed genes means that any mutations within the replicated DNA will be expressed more frequently[73,74]. At the same time, telomere shortening reduces the production of enzymes that delay cell senescence, apoptosis, and decrease susceptibility to genetic mutations[75-78]. Researchers reported a correlation between telomere shortening and decline in stem cell function as people age[75,76]. Another study inversely proved that mice overexpressing telomeres showed that mice with longer telomeres had delayed aging and increased cancer resistance[79].

As cells are always exposed to the environment, they continuously accumulate oxidative stress throughout their life [73]. Derangement may then be passed on to the next generation of cells: Causing transcription, translation, and proofreading to fail during DNA synthesis. This perpetuates to form a cycle where cells live to continuously accumulate derangements, only to be passed on later to the next generation of cells[73]. This explains why 'degenerative' diseases become more apparent as we age[73]. This process is called a somatic mutation, described as cellular level alteration in somatic tissues occurring after fertilization that does not involve the germline and consequently does not carry on to the offspring[80].

Exploring the root cause of DNA damage further, scientists have discovered that oxidative stress played a key role in causing derangements of the molecular composition within amino acids that form the DNA chain[80,81]. Oxidative stress occurs due to an imbalance between reactive oxygen and nitrogen species and antioxidants within the body[80-82]. It may be obtained internally as a byproduct of metabolism (which includes pathogen-caused inflammation) and externally from the environment. Eventually, these mutations can evolve from silent mutations into diseases deemed clinically significant [80-82].

However, the occurrence of thrombotic events, particularly in young people, should warrant screening for blood cancers and especially MPNs. Mayerhofer *et al*[83] highlighted that young individuals who experience episodes of stroke display a three-times elevated prevalence of clonal hematopoiesis of indeterminate potential mutations and several suffer from MPNs and eventually need of cytoreduction treatment. Furthermore, they defined that these patients express a higher burden of atherosclerosis and an elevated carotid intima media thickness, reinforcing that there is pronounced endothelial dysfunction in MPNs[83,84]. It is well known that dyslipidemia aggravates atherogenesis and is associated with inflammation, oxidative stress, cytokines, and other molecular messengers to promote atherosclerosis, including in subjects with MPNs[85-87]. We have learned from murine models that laboratory mice that express the *JAK2V617F* mutation and suffer from dyslipidemia exhibit a myriad of aberrant molecular mechanisms that aggravate atherosclerosis, namely macrophage erythrophagocytosis, increased lipid peroxidation, p38 mitogen-activated protein kinase signaling and concentrations of pro-inflammatory chemokines, RBC-derived microvesicles and cytokines, endothelial damage, defective efferocytosis, inflammasome overactivation, ferroptosis, decreased levels of c-Mer tyrosine kinase, and expansion of preleukemic HSCs[88-91]. ATP-binding cassette sub-family G member 1 and ATP binding cassette subfamily A member 1, *i.e.* adenosine triphosphate-binding cassette transporters, N-acetyl cysteine, fedratinib, HDL-C, and simvastatin seem to alleviate atherogenesis, myelopoiesis, and endothelial dysfunction in *in vivo* assessments of *JAK2V617F*-positive mice[90,92,93]. These findings have been confirmed by investigations conducted in MPN subjects, as Skov *et al*[94] pointed out that in MPNs, there is a dysregulation of several genes involved in the development of athero-

sclerosis, for example downregulation of B-cell lymphoma 2 (Bcl-2) and upregulation of matrix metalloproteinase 1, Bcl-2-like protein 1, thrombospondin-4, and prostaglandin-endoperoxide synthase 1 is in PV, ET, and PMF[94]. Moreover, elevated variant allele frequencies of *JAK2V617F* and neutrophil-to-lymphocyte ratios are associated with notable inflammation, arterial stiffness, and atherosclerosis in MPNs[95-97]. Furthermore, in subjects with atherosclerosis, dyslipidemia is associated with increased concentrations of platelet-derived growth factor and other cytokines which are molecules known to stimulate proliferation of myeloid cells, and peripheral arterial disease, a vascular complication driven by lipid abnormalities and atherogenesis, has been shown along with atrial fibrillation to be a notable predictor of thrombotic and bleeding complications, as well as death in MPNs[98,99]. Thus, the crosstalk between dyslipidemia, inflammation, and oxidative stress may stimulate a process of accelerated atherosclerosis in MPNs and eventually results in higher rates of thrombotic and, in some cases, hemorrhagic complications in these hematological malignancies (Figure 1)[100].

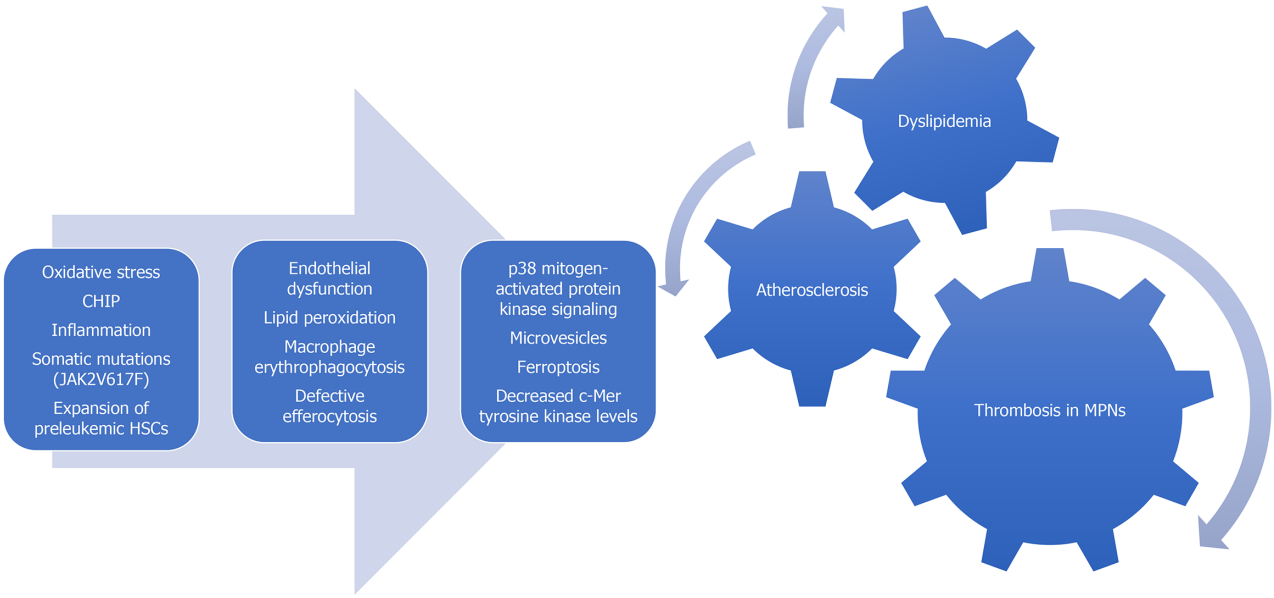

Figure 1 Schematic representation of the interplay among dyslipidemia, atherosclerosis, and myeloproliferative neoplasms, with a focus on the main pathogenetic mechanisms that drive the development of atherosclerosis. CHIP: Clonal hematopoiesis of indeterminate potential; HSC: Hematopoietic stem cells; MPNs: Myeloproliferative neoplasms.

CONCLUSION

Lipid abnormalities trigger the development of atherosclerosis and work together with oxidative stress, inflammation, genetics, and a conundrum of molecules to increase the risk of thrombosis in MPNs. In addition, several drugs used in the treatment of these blood cancers, such as ruxolitinib or interferon-alpha, may alter the lipid profiles of MPN subjects. Thus, the interaction between dyslipidemia and MPNs appears complex and requires in-depth research in future studies that should evaluate the impact of dyslipidemia as a unique and potentially deleterious CVRF in these hematologic malignancies.

FOOTNOTES

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