

# **THROMBOTIC EVENTS IN MYELOPROLIFERATIVE NEOPLASMS COULD “MEDICAL NUTRITION THERAPY” HAVE AN ADDITIONAL BUT IMPORTANT ROLE?**

*Éva Pósfai*

Albert Szent-Györgyi Clinical Center - University of Szeged, H-6720 Szeged, Korányi fasor 6. Hungary  
e-mail: evaposfai@gmail.com

## **ABSTRACT**

Polycythemia vera (PV), and essential thrombocythemia (ET) patients are characterized by an increased incidence of arterial and venous thromboses. To prevent vascular events is one of the most important challenges in the disease management, as thrombosis could be responsible for the morbidity and mortality in many cases. Since thrombosis can be an early complication of MPNs, an effective antithrombotic strategy has to be started as soon as the disease is diagnosed. Beside the use of appropriate medical therapies and preventive measures against cardiovascular risk factors, a healthy lifestyle may also have importance in MPNs, as it has already been accepted in the general population. However, it has not been accepted yet in the treatment of neoplasms, according to the general notion, thrombosis is "caused" by the disease rather than by the interplay of various factors. The relation between the disease and the thrombotic events is indisputable, though the role of the neoplasm accompanied by other diseases such as diabetes mellitus, cardiovascular diseases, or unhealthy life style, obesity, and smoking should be mentioned as addictive factors in case of myeloproliferative neoplasms thus increasing the susceptibility to developing a thrombosis. In this short communication, according to relevant medical literature, the author describes her concerns if cardiovascular diseases may be prevented by eliminating modifiable risk factors, and following a healthy diet, healthy life style and controlling body weight, and whether it may have an important benefit in the successful management of MPN patients. Should we apply the “medical nutrition therapy” consciously in the most appropriate and effective antithrombotic strategy?

## **1. INTRODUCTION**

Philadelphia Chromosome “negative” myeloproliferative neoplasms (MPN) is a diverse group of hematological malignancies. MPNs are characterized by stem cell-derived clonal myeloproliferation primarily characterized by erythrocytosis and thrombocytosis with predisposition to thrombosis, bleeding, and the possibility of leukemic transformation. Polycythemia vera (PV) and essential thrombocythemia (ET) patients are characterized by an increased incidence of arterial and venous thromboses and by microcirculatory disturbances which often manifest in the diagnosis or in the preclinical phase of the disease. (Michiels, Abels et al. 1985) To prevent a significant number of early vascular events is still one of the most important challenges in the disease management, because thrombosis could be a major cause of morbidity and mortality in patients in many cases. (Tefferi 2012) Thus an effective antithrombotic strategy has to be started as soon as the disease is diagnosed. According to the international protocols, this strategy mostly includes treatment in different combination of low-dose aspirin, clopidogrel bisulfate, hydroxyurea, and interferon therapy. Phlebotomy also could be used accordingly as a risk adapted decision. (Vladareanu 2010)

## **2. SUMMARY OF THE RELEVANT LITERATURE**

Several epidemiological studies performed in the field of the nutrition and physical activity of the general population are predictors of age-specific mortality and cardiovascular events. The connection between cardiovascular risk factors and

thrombosis is not doubted any more, and the identification and appropriate management of cardiovascular risk factors, the promotion of a healthy lifestyle in the general population have become important and popular. According to the World Heart Federation's opinion: (Bas, Altan et al. 2005;Poirier, Giles et al. 2006Waskiewicz, Piotrowski et al. 2008) "The role of diet is crucial in the development and prevention of cardiovascular diseases. Diet is one of the key things you can change that will impact all other cardiovascular risk factors." Table 1 introduces the modifiable risk factor which could be important according to the World Heart Federation's opinion.

**Table 1. Risk factors associated with coronary heart disease and stroke according to the World Heart Federation**

<i>Modifiable risk factors</i>	<i>Non-modifiable risk factors</i>
Hypertension	Age
Abnormal blood lipid levels	Gender
Tobacco	Ethnicity
Physical inactivity	Family history of cardiovascular diseases
Type 2 diabetes	
Diet high in saturated fat	
Chronically stressful life	
Social isolation	
Anxiety and depression	
Contraceptive pills	
Hormone replacement therapy	

Source: World Heart Federation (2012)

But what about patients with MPNs? Does diet have as important a role as in the general population? On the contrary, the importance of a healthy lifestyle is frequently misjudged in MPN patients due to the tendency to consider thrombosis as it has been "caused" by the disease rather than by the interplay of various factors. ECLAP is a randomized trial (European Collaboration on Low-dose Aspirin in Polycythemia Vera ), which has many observations to support the idea that besides the basic medical antithrombotic strategy, we have to focus more on the modifiable risk factors in MPN patients as well. According to the publication of Finazzi G. in 2004, the cumulative incidence rate of cardiovascular events (i.e., cardiovascular death and non-fatal thrombotic events) was 5.5 events/100 persons per year. The main cause of death was thrombosis. Their results showed that the two most important predictors of cardiovascular events were age (higher than 65 years) and positive history of thrombosis. Nevertheless, they have found smoking, hypertension and congestive heart failure to be further significant risk factors for thrombosis.(Finazzi 2004) In the same trial in 2007, Landolfi et al. also described smoking as a habit that had an important effect on vascular risk associated with a significantly higher risk of arterial thrombotic events, and not just in the general population but among PV patients as well. A similar finding had been reported also in ET subjects by Besses et al. in 1999 and Jantunen in 2001. (Besses, Cervantes et al. 1999; Jantunen, Juvonen et al. 2001) Additionally, the ECLAP observational study has shown that diabetes was a possible predictor of survival and cardiovascular mortality in MPN patients. According to the above mentioned studies, it is supposed that arterial hypertension, hypercholesterolemia, obesity and metabolic syndrome, the well-known major risk factors for the development of

cardiovascular diseases in the general population, could have an important role as the predictors of thrombosis in MPN patients despite the limited results. But surprisingly, we could find publications which rather contradicted the above mentioned notions. A few clinicians like Besses have found that ET patients demonstrated the independent contribution of hypercholesterolemia in predicting thrombosis. (Besses, Cervantes et al. 1999) According to the relevant literature, the efficacy of statins in MPNs has yet to be tested in prospective studies, but their possible use in MPNs deserves clinical and scientific attention. In the view of nutrition, epidemiological studies and clinical trials indicate the importance of nutrition. In a prospective study, over 12 years, 14,962 middle-aged adults participating in the Atherosclerosis Risk in Communities Study were followed up for incident VTE. According to their conclusion, it could be supposed that diet including more plant food and fish, and less red and processed meat could be associated with a lower incidence of venous thromboembolism. (Lichtenstein, Appel et al. 2006) The very long chain n-3 fatty acids lower the thrombotic tendency and risk of heart diseases. Other polyunsaturated fats and monounsaturated fat appear to have antithrombotic properties, but further studies are needed to reveal it. (Lands, Libelt et al. 1992) Low intake of folate, vitamin B12, and vitamin B6 predispose patients to hyperhomocysteinemia, and the benefits of their supplementation in decreasing vascular diseases are under investigation.(Erzin, Uzun et al. 2008) Dietary flavonoids like apigenin and luteolin, and isoflavones like genistein appear to inhibit platelet aggregation only in pharmacological concentrations. (Clair and Anthony 2005) (Liu, Xing et al. 2006) Among the group of flavonoids, apigenin is very interesting as Navarro-Nunez L's results demonstrate a clear increase in the ex vivo antiplatelet effect of aspirin in the presence of apigenin, which encourages the idea of the combined use of aspirin and certain flavonoids in patients, in whom aspirin fails to properly suppress the TxA(2) pathway. (Navarro-Nunez, Lozano et al. 2008) As we can see, diet presents an interesting area for research also in the field of general medicine, but work is indicated before specific recommendations are made. (Allman-Farinelli and Dawson 2005) According to the relevant literature in myeloproliferative neoplasms, the suspected factors could play an important role in the development of thrombosis in MPN patients, as a conclusion showed in Table 2.

**Table 2. Factors that are suspected to play an important role in the development of thrombosis in MPN patients**

<i>Disease related abnormalities</i>	<i>Cardiovascular risk factors</i>
Hyperviscosity Leukocyte abnormality Platelet abnormality Inflammation JAK2 V617F mutation	Obesity Diabetes Hypertension Smoking Unhealthy diet
<i>Other factors</i>	Lack of physical activity
Previous thrombosis Age Gender Other genetic mutations Other unknown factors, local, general triggers	

Source: World Heart Federation (2012)

### 3. CONCLUSIONS

The American Dietetic Association introduced a new aim in 2010, the goal of which is the integration of "Medical Nutrition Therapy (MNT) and Pharmacotherapy" and introduced many guidelines as in diabetes mellitus, summarizing the evidence for the effectiveness of MNT in preventing and treating diabetes, and providing physicians with information on how to refer patients to MNT. The initiation and ongoing use of medical therapy is essential in myeloproliferative patients to prevent the development of disease complications and to manage the disease appropriately. As the life expectancy of patients in adequate condition is very promising, the survival years can reach up to several decades. Although the most frequent cause of death is patients is thrombosis, it is an interesting question whether conscious life style of these patients can lead to the achievement of a more beneficial therapy and whether thrombotic events may be prevented to a certain extent (parallel to medical therapy), thus achieving a longer life span. Conscious, healthy nutrition has an unequivocal role in preserving vascular intactness, and therefore, further investigation is needed in this topic. It is also vital to encourage patients to follow a healthy lifestyle. Nevertheless, its possible use in MPNs deserves clinical and scientific attention. Therefore, diet as one of the environmental factors has an impact on the development of thrombosis and hemostasis, and macronutrients, micronutrients, and other bioactive food components may alter the predisposition to thrombosis. However, in many cases such as the management of diabetes, the evidence is strong that medical nutrition therapy provided by registered dietitians is an effective and essential therapy, but in MPN neoplasms no strong evidence has been established yet. Though according to the known details, this notion should not be neglected, especially in the view of controlling risk factors.

### REFERENCES

1. Allman-Farinelli, M. A. and B. Dawson (2005). "Diet and aging: bearing on thrombosis and hemostasis." *Semin Thromb Hemost* **31**(1): 111-117.
2. Bas, M., T. Altan, et al. (2005). "Determination of dietary habits as a risk factor of cardiovascular heart disease in Turkish adolescents." *Eur J Nutr* **44**(3): 174-182.
3. Besses, C., F. Cervantes, et al. (1999). "Major vascular complications in essential thrombocythemia: a study of the predictive factors in a series of 148 patients." *Leukemia* **13**(2): 150-154.
4. Clair, R. S. and M. Anthony (2005). "Soy, isoflavones and atherosclerosis." *Handb Exp Pharmacol*(170): 301-323.
5. Erzin, Y., H. Uzun, et al. (2008). "Hyperhomocysteinemia in inflammatory bowel disease patients without past intestinal resections: correlations with cobalamin, pyridoxine, folate concentrations, acute phase reactants, disease activity, and prior thromboembolic complications." *J Clin Gastroenterol* **42**(5): 481-486.
6. Finazzi, G. (2004). "A prospective analysis of thrombotic events in the European collaboration study on low-dose aspirin in polycythemia (ECLAP)." *Pathol Biol (Paris)* **52**(5): 285-288.
7. Jantunen, R., E. Juvonen, et al. (2001). "The predictive value of vascular risk factors and gender for the development of thrombotic complications in essential thrombocythemia." *Ann Hematol* **80**(2): 74-78.
8. Lands, W. E., B. Libelt, et al. (1992). "Maintenance of lower proportions of (n - 6) eicosanoid precursors in phospholipids of human plasma in response to added dietary (n - 3) fatty acids." *Biochim Biophys Acta* **1180**(2): 147-162.

9. Lichtenstein, A. H., L. J. Appel, et al. (2006). "Summary of American Heart Association Diet and Lifestyle Recommendations revision 2006." *Arterioscler Thromb Vasc Biol* **26**(10): 2186-2191.
10. Liu, R., D. Xing, et al. (2006). "Pharmacokinetics of puerarin and ginsenoside Rg1 of CBN injection and the relation with platelet aggregation in rats." *Am J Chin Med* **34**(6): 1037-1045.
11. Michiels, J. J., J. Abels, et al. (1985). "Erythromelalgia caused by platelet-mediated arteriolar inflammation and thrombosis in thrombocythemia." *Ann Intern Med* **102**(4): 466-471.
12. Navarro-Nunez, L., M. L. Lozano, et al. (2008). "Apigenin inhibits platelet adhesion and thrombus formation and synergizes with aspirin in the suppression of the arachidonic acid pathway." *J Agric Food Chem* **56**(9): 2970-2976.
13. Poirier, P., T. D. Giles, et al. (2006). "Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism." *Circulation* **113**(6): 898-918.
14. Tefferi, A. (2012). "Polycythemia vera and essential thrombocythemia: 2012 update on diagnosis, risk stratification, and management." *American Journal of Hematology* **87**(3): 284-293.
15. Vladareanu (2010). "Molecular markers guide diagnosis and treatment in Philadelphia chromosome-negative myeloproliferative disorders (Review)." *Oncology Reports* **23**(3).
16. Waskiewicz, A., W. Piotrowski, et al. (2008). "Quality of nutrition and health knowledge in subjects with diagnosed cardio-vascular diseases in the Polish population--National Multicentre Health Survey (WOBASZ)." *Kardiol Pol* **66**(5): 507-513, discussion 514.