



Summary

Perioperative comparison of laboratory parameters in diabetic and non-diabetic patients having lower limb surgery during the COVID-19 pandemic

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Peripheral arterial disease (PAD) affects over 110 million people over 40 years of age globally, its prevalence has been increasing in recent decades. The disease can be asymptomatic for a long time, after which intermittent claudication occurs. In patients with diabetes mellitus, claudication occurs twice as frequently and the mortality from this condition is double compared to non-diabetic subjects.

Comprehensive investigation of PAD patients could contribute to the identification of subjects at high risk for complications and prolonged hospitalization. These more vulnerable patients could benefit from additional perioperative measures in order to improve the chances of a favorable outcome, using personalized therapeutic regimens. Inflammatory markers can provide clinicians with information about the inflammatory process that often accompanies vascular pathology, the process being intensified by the presence of diabetes mellitus.

In the first study, a comprehensive evaluation of overweight and obese patients with type 2 diabetes mellitus (T2DM) was performed, considering the chronic inflammation related to glucose metabolism disorders and excess weight. The aim was to identify cardiovascular risk factors using metabolic laboratory analyses, including derived parameters, interpreted in close connection with clinical aspects. One third of overweight or obese patients with type 2 diabetes mellitus had elevated serum uric acid levels, and more than half had dyslipidemia. Derived ratios (triglyceride/glucose ratio, cholesterol/triglyceride ratio) revealed pathological values compatible with insulin resistance and an increased cardiovascular risk in over one third of the patients. We observed strong correlations between several laboratory markers, reflecting imbalances in metabolic pathways. Targeting abnormal laboratory markers is essential for implementing secondary prevention strategies, especially for reducing cardiovascular complications, the risk being the highest in patients presenting multiple predisposing factors (diabetes mellitus associated with excess weight, hypertension, dyslipidemia and smoking).

In the second study, diabetic and non-diabetic patients with peripheral arterial disease were investigated comparatively, using laboratory analyses (including metabolic parameters, serum homocysteine level, numerous common and special inflammatory markers, a genetic thrombophilia test for the MTHFR (methylene tetrahydrofolate reductase) gene mutation and microbiological investigations) corroborated with clinical evolution. The duration of hospitalization was significantly shorter in patients in whom all blood count-derived inflammatory markers were within the normal range compared to those who had at least one pathological value for these parameters. The homocysteine level was significantly higher in patients with homozygous mutation of the MTHFR gene



compared to those who had the wild-type allele. The most common germ in wet gangrene was *Staphylococcus aureus*. Over one third of the Gram-negative strains isolated showed multidrug resistance. Lower hemoglobin and lymphocyte-monocyte ratio (LMR) values were found in subjects with T2DM compared to non-diabetic patients.

The third study dynamically followed the evolution of metabolic and inflammatory parameters, besides malondialdehyde (MDA) as a marker of lipid peroxidation in the perioperative period in diabetic and non-diabetic patients with peripheral arterial disease who required surgery, the laboratory analyses being interpreted in the context of the clinical evolution. Serum malondialdehyde has increased values in patients with chronic diseases especially after surgery, the intensity of oxidative stress showing a positive correlation with the inflammatory process. Dynamic evaluation of inflammatory markers is suitable for monitoring the outcome of patients undergoing surgery. Preoperative IL-6 (interleukine-6) concentrations were critical in a quarter of the study group and moderately increased in half of the subjects. There was a significant difference in IL-6 levels at postoperative follow-up in the diabetic subgroup compared to the non-diabetic one. The predictive value of preoperative IL-6 was observed, as subjects with levels above 35 pg/ml mostly required hospitalization longer than 2 weeks. Measurement of multiple inflammatory markers (IL-6, CRP) and biochemical parameters may be useful in identifying patients prone to complications, who may benefit from more complex management.

This doctoral thesis represents an interdisciplinary approach to the pathology related to PAD in diabetic and non-diabetic patients, encompassing clinical aspects related to disease staging, patient selection and surgical interventions such as lower limb amputations corroborated with the perioperative evolution investigated by various common paraclinical measurements and research tests. A wide range of laboratory methods were used: photometric, turbidimetric, ELISA, real-time PCR (polymerase chain reaction), coagulometry, flow cytometry, chromatographic, microscopic, cultivation and diffusimetric methods. The studies in the thesis involve a series of special laboratory parameters in the field of inflammatory markers, such as the dosage of pro-inflammatory cytokines IL-6 and TNF- α (tumor necrosis factor alpha), and parameters derived from the blood count, including the platelet-monocyte ratio (PMR), an inflammatory marker less used in practice.

In addition to these biochemical and hematological markers, the microbiological results of samples collected from wet gangrene were also processed, the incursion into the identification of strains and their resistance to antibiotics increasing the complexity of the thesis.

The test on the MTHFR gene mutation brings another note of complexity and originality to the thesis, the results being corroborated with the dosage of serum homocysteine, its increased values being correlated with the risk of thrombosis. The present work is among the few studies on some markers within the thrombophilia profile in subjects with peripheral arterial disease. Among the oxidative stress parameters, serum MDA dosage was used, the HPLC method used being an original one, developed and implemented by our research team, the results being corroborated with inflammatory markers. A note of originality is the perioperative dynamic evaluation of laboratory parameters (upon admission and two days after the surgical intervention), offering the possibility of identifying prognostic factors for the evolution.