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PhD THESIS

SUMMARY

CLINICAL, METABOLIC, AND ECHOCARDIOGRAPHIC CORRELATIONS IN PATIENTS WITH HEART FAILURE, HYPERURICEMIA AND CHRONIC KIDNEY DISEASE

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Heart failure is an entity that includes an increased variety of clinical phenotypes with different manifestations and evolution from case to case, even if the damage seems similar both from a clinical standpoint and from an objective evaluation standpoint.

All projections of international organizations foresee an increase in the number of heart failure cases, both in the medium and long term, so that by the fourth decade of this century, the incidence of heart failure regardless of its form is expected to be around 3.5%; the increase compared to the first decade of the century is about 2% in absolute percentage.

The research topic of this PhD thesis is to evaluate the impact of risk factors on heart failure where there is still controversy in the specialized literature, the main factor studied being uric acid. The purpose of this research is to assess whether there is a link between risk factors, ejection fraction and clinical, biological, and echocardiographic parameters in patients with heart failure, classified according to the recommendations of the European Society of Cardiology. The objectives of this paper are to conduct retrospective observational clinical trials to prove that the impact of uric acid is different, depending on the clinical profile and the ejection fraction of heart failure, this thesis consisting of two clinical studies in which patients with heart failure (depending on uric acid levels) and patients with severe chronic kidney disease were compared and evaluated, given that uric acid is an easily dialysable product.

In cardiovascular pathology, uric acid is frequently overlooked, either by omitting the dosing of this metabolite or if hyperuricemia is asymptomatic, by considering it not to be of therapeutic interest. The recommended therapeutic interventions do not have an indication class, phrases such as ”it is possible to bring benefits” being used. This requires extensive and long-lasting clinical studies that clearly establish the connection between the two entities.

From a genetic point of view, the relationship between cardiovascular disease and hyperuricemia is controversial, although it has been established

that there is an increase in cardiovascular risk, but whether the influence is mutual or not or whether the relationship is cause and effect, including bidirectional, is still a topic where fundamental research is still a necessity. Mendelian randomization studies superimposed in GWAS studies and CHARGE meta-analysis showed that the genetic score of urate and, not necessarily, the level of serum uric acid were responsible for cardiovascular events. The CHARGE meta-analysis consisted of the analysis of 5 GWAS studies, totaling over 28,000 patients, showed that 2 loci [SCL2A9 and ABCG2] are responsible for the association with symptomatic hyperuricemia, with an odds ratio of 12.4 for every 1.68mg/dl (100µmol/L) and are not associated with hypertension (HTN), glucose levels or chronic kidney disease (CKD).

This acid is the final product of the catabolism of purine bases in humans, primates, reptiles, and birds. In some mammals, uric acid is further degraded to an even more soluble product, allantoin, resulting from the exposure of uric acid to the action of uricase. In the course of evolution, the superior primates, including humans, lost the uricase enzyme, the metabolism stopping at the level of uric acid. Also, Chung et al cites a work by Proctor from the 1970s, in which the ability to synthesize ascorbic acid was also lost, so that uric acid took over some of the antioxidant and electron donation capacity (deoxidizing capacity) of ascorbic acid. In humans over 50% of the antioxidant capacity of blood plasma is given by hydrates of urate ions (uric acid).

Heart failure is one of the main diseases with major impact on all levels, both at individual level and at society level. Latest update (Heart Disease and Stroke Statistics – 2021 Update) on cardiovascular disease and vascular attack of the American Heart Association (AHA) under the coordination of Virani et al [publishes worrying figures. Data derived from NHANES studies (National Health and Nutrition Examination Survey) reveal that about 2% of the adult United States population has heart failure. In absolute figures these translate into an increase of 300,000 new cases between 2015 and 2018 compared to the period 2009 – 2012.

Equally worrying is the projection carried out under the coordination of Heidenreich et al which shows an increase in prevalence by 0.6 percentage by 2030, which would add another 2 million new cases, taking into account the natural increase.

Patients with heart failure present both traditional risk factors and, more recently, identified risk factors, a whole series of articles with major impact on the evaluation of risk factors being published in this regard.

While traditional risk factors such as hypertension, diabetes, obesity, smoking or coronary artery disease account for more than half of the causes of heart failure identified by the study in Olmsted County, Minnesota [29], data from NHANES reveal that at least one-third of adults have at least one risk factor for heart failure.

The new European Society of Cardiology (ESC) guideline published in 2021 cited by Huffman et al still uses as a cornerstone in the diagnosis of heart failure the specific signs and symptoms, which are found in all 3 types of heart failure, by considering the measurement of the left ventricle ejection fraction as an additional criterion for quantification. In the case of heart failure with retained ejection fraction, objectification of the structural cardiac damage is additionally required, along with the use of natriuretic peptides as another marker of cardiac dysfunction.

The involvement of uric acid in heart failure is still a hotly debated topic. There are studies that suggest the need for treatment even in asymptomatic situations of hyperuricemia, but there are also studies that suggest increased risks associated with treatment with hypouricemia drugs. High levels of uric acid are associated with hypertension, atherosclerosis, atrial fibrillation, and heart failure . Experimental studies have shown that the development of cardiovascular diseases in hyperuricemia are secondary to the initiation of molecular signaling pathways involving inflammatory response, increased axial stress, insulin resistance or endothelial dysfunction

A meta-analysis of Huang et al conducted following the identification of 33 clinical trials, of which 28 looked at side effects adverse to cardiac insufficiency, showed that increased serum uric acid is associated with a weaker prognosis. This meta-analysis showed a dose-response relationship, so an increased uric acid is a predictor of overall mortality, cardiovascular mortality, and worsening heart failure. One conclusion showed that mortality increases by 13% for every 1 mg/dL increase in uric acid above the reference value of 7 mg/dL.

The European Society of Cardiology (ESC) is one of the important profile companies that grants a section dedicated to uric acid and hyperuricemia in its own heart failure guide, being currently one of the most comprehensive and detailed guidelines that address the problem of hyperuricemia in heart failure.

The latest ESC Guideline published in 2021 assigns a prevalence of approximately 50% of hyperuricemia in these patients, considering hyperuricemia as a negative prognostic factor. The treatment recommendation in the absence of contraindications is to use allopurinol as the first therapeutic option, which showed its non-inferiority to febuxotat in a prospective study that enrolled over 6,000 patients.

The objective of this PhD Thesis is to evaluate the risk factors, the clinical profile, and the clinical evolution of patients with heart failure and hyperuricemia, with and without renal damage, in order to highlight hyperuricemia both as a marker of cardiac damage and as a negative prognostic factor, by reference to echocardiographic parameters.

The current paper contains two clinical trials that compare patients with heart failure between the component groups. The first study compares a group of over 303 patients with heart failure with low ejection fraction, patients with heart failure and slightly reduced ejection fraction, and patients with preserved ejection fraction. The second clinical trial includes a group of 61 patients with severe chronic kidney disease requiring kidney supplementation therapy in the form of chronic hemodialysis that also have heart failure with different ejection

fraction levels, who are characterized from a clinical and echocardiographic standpoint.

Clinical trial number 1 is a study whose purpose study is to evaluate the relationship between the SUA (serum uric acid) and heart failure, classified according to the guidelines of the European Society of Cardiology, in a region of Europe characterized by a high prevalence of cardiovascular diseases, obesity and diabetes mellitus. A retrospective analyse of a series of 303 consecutive patients with known heart failure, admitted to the Internal Emergency Medicine Department of the Municipal Emergency Clinical Hospital from Timisoara was performed. The statistical analysis for this clinical trial was based on unidirectional ANOVA tests for continuous variables and Chi-square tests for categorical variables, the corresponding p-values being presented in the summary tables. Comparisons in pairs were made based on significance tests by Bonferroni analysis, with reporting of the corresponding significance (S) ($p \leq 0.05$) or non-significance (NS. $p > 0.05$). A statistically significant difference in the average value of serum uric acid results was observed between patients in the categories with FE >50% and FE <40%. Patients in the group with FE >50% had significantly lower uric acid compared to the group of patients with FE <40%. A statistical difference was observed between patients in the group of patients with FE 49-40% and FE <40%, with patients in the group with FE 49-40% having a significantly lower uric acid compared to the group of patients with <40% systolic ejection fraction

Current population changes show an increase in the pefHF incident, with the results obtained in this study confirming that the proportion of patients with pefHF is higher than the proportion of patients with mrHF and refHF. The meta-analysis of Carraballo et al shows that there is a trend towards increasing the proportion of patients with pefHF and their increased heterogeneity, while the meta-analysis of Hao et al shows an increase in the total incidence of heart failure with low control of risk factors such as high blood pressure or suboptimal treatment.

Regarding the uric acid, statistically significant results were highlighted between the studied groups. Patients in the pefHF group had a lower SUA level compared to those in groups with an ejection fraction between 40 – 49% and <40%. One of the possible explanations results from the pathophysiological changes that occur with the reduction of the ejection fraction, and lead to the increase of the SUA ; however, the uric acid being a product of purine catabolism is involved through other possible mechanisms . Huang et al showed that in addition to increased cardiovascular mortality of patients with hyperuricemia, mortality of any cause is also increased by 4% for each 1 mg increase in serum uric acid.

In the current study, the vast majority of patients with mrHF (≈ 40%) were identified as belonging to the NYHA II class, Piepoli et al suggesting that patients with moderate to severe heart failure classified in NYHA classes I and II had a uric acid that was statistically significant associated with cardiovascular mortality, while patients in grade III and grade IV, respectively, did not have a higher risk.

By using a linear regression, we obtained a significant model ($p = 0.030$) in which the EF variability is expressed by uric acid in the proportion of about 1.5% (R-square = 0.015). Therefore, a significant link between the LVFF and uric acid was revealed.We also achieved significant results when a linear regression model ($p = 0.004$) was calculated, where log NT-proBNP variability is expressed by uric acid in the proportion of approximately 2.7% (R-square = 0.027). Therefore, a significant link between NT-proBNP levels and serum uric acid was revealed .A significant linear regression model ($p < 0.001$) was obtained between the ELFF variability expressed by BNP in a proportion of approximately 37.0% ($R2 = 0.376$).By linear regression we have refrained from another statistically significant model ($p < 0.001$) in the case of patients with pefHF in which the variability of eGFR is expressed by uric acid is in a proportion of about 19.3% ($R2 = 0.193$).

One of the limitations identified is that this is a retrospective study, although the number of patients (>300) included would be sufficient for an adequate statistical power. The lack of successive measurements of uric acid level can contribute to limiting the significance of some results. Also, the exclusion of patients with diuretic medication, especially thiazide-like only, may not be enough because other drugs can contribute to the false increase of uric acid levels, along with non-reporting by patients included in the observation sheets of other classes of drugs that can induce hyperuricemia.

The second study consisted of another retrospective study which included61 patients with chronic kidney disease in various forms of renal suppletion who were echocardiographically diagnosed with heart failure with moderately reduced ejection fraction (mrHF) and retained ejection fraction (pefHR). Also, uric acid is a product eliminated by the dialysis process in a significant proportion, which should attenuate from its detrimental effects by maintaining a plasma concentrate as low as possible and without presenting significant oscillations.

Following the analysis and based on the demographic characteristics, the patients were predominantly men, with an average age of about 50 years-old, with a dialysis duration of at least 3 years, hypertensive in overwhelming proportion and with a fairly high proportion of diabetics. Also, in terms of treatment, most of them were following treatment with converting enzyme inhibitors, beta blockers, antiplatelet diuretics and calcium channel blockers, a smaller proportion of patients undergoing statin treatment.

The comparison between the two groups with heart failure with and without cardiovascular events did not show significant differences in terms of gender, age, body mass index, high blood pressure, or smoking history, but statistically significant results were observed in the case of diabetes mellitus and history of cardiovascular disease prevalence. The level of total cholesterol was still insignificant.

Although some authors consider the fact that altered renal function is an aggravating factor of heart failure, some authors such as Mascarenhas and collaborators consider that kidney function is rather a marker of heart disease, because although the filtration rate was progressively decreasing within the analyzed group, the comorbidities and objective signs of cardiac damage explained more correctly the deficient prognosis by multivariate analysis. Chan and co-authors note that, although reducing end-diastolic and end-systolic volumes, as well as the ventricular mass in patients with chronic hemodialysis, the actual remodeling process is not affected, which could explain on the one hand the mortality and the poor prognosis of these patients. The association with other renal abnormalities of heart failure, such as albuminuria, was evaluated by Nayor et al], the authors suggesting that microalbuminuria was associated with the risk of developing refHF and with systolic dysfunction, but chronic kidney disease was moderately associated with, without a significant difference about the strength of the association between refHF and pefHF.

Establishing the risk profile for this special population requires additional studies for which, indeed, the duration of hemodialysis, as well as the association with multiple comorbidities can be even higher, depending on the cardiovascular profile.

Most of the patients included in this study had a medium-level ejection fraction and a preserved ejection fraction. It remains to be determined to what extent the ejection fraction contributes to the overall risk, the survival rate, and the duration of dialysis and its effectiveness. The new Tissue Doppler and speckle tracking techniques can add more prognostic value for us to understand and treat the dialysis patient, involved in the pathophysiological continuum between the kidneys and the heart .

The exclusion of uric acid levels from the analysis can even be considered the main limitation of this study, since the possible cardiovascular damage caused by uric acid until the initiation of renal suppleness therapy is not considered, which cannot necessarily be denied. The small group of patients

and, especially, those with cardiovascular events, which can contribute to the statistical power and the insignificance of certain parameters, such as for example the tele-diastolic diameter, may be considered as the second limitation identified.

The fact that the multivariate analysis, especially on the medication, did not reveal any significance, probably due again to the small number of cardiovascular events, can also be considered a limitation

The main objective of this work was to detail the impact of a risk factor, hyperuricemia, in patients with heart failure, with and without associated kidney disease, because this risk factor is often overlooked.

Hyperuricemia in heart failure is a risk factor, as well as the effect of the detrimental metabolic processes that the decrease in the ejection fraction produces in the long term.

The main conclusion is that uric acid is a sensitive marker of cardiovascular damage in patients with heart failure, cardiac structural damage and metabolic suffering induced by the decrease in the ejection fraction translating into its increased levels.

The important problem remaining is how uric acid can be introduced into risk calculation scores of major cardiovascular events in heart failure, there still being multiple situations where it grows outside of heart failure, but which can provide false negative results. Also, the association with chronic kidney disease, especially in the category of patients with advanced renal impairment, uric acid can be both a cause and an effect of cardiovascular events.

The general conclusions of the present work will be summarized during the following pages, by pointing out the main results of my own research:

- The male gender shows more severe phenotypes of heart failure, refHF predominating
- Diabetes mellitus is a risk factor associated to heart failure, which is more associated with diastolic and pefHF dysfunction

- The lipid profile in patients with heart failure suggests the direct link between atherosclerosis and the ejection fraction; patients with higher ejection fractions have a lower level of LDL-cholesterol
- The lipid profile in patients with heart failure suggests the direct link between atherosclerosis and the ejection fraction; patients with smaller ejection fractions have a lower level of HDL-cholesterol
- The lipid profile in patients with heart failure suggests the direct link between atherosclerosis and the ejection fraction; patients with larger ejection fractions have a lower serum triglyceride level
- As the ejection fraction decreases, the volume of the left atrium increases, even in the absence of atrial fibrillation
- Natriuretic peptides (NTproBNP) increase as the ejection fraction decreases
- Uric acid increases the most in patients with mrHF and refHF
- Uric acid correlates positively with the levels of natriuretic peptides; at increased levels of uric acid, natriuretic peptides are more likely to be increased
- The ejection fraction of the left ventricle correlates directly with the increased serum level of uric acid; between the two parameters the correlation is inversely proportional
- Kidney damage is associated with an increase in uric acid in a directly proportional way, the more severe the glomerular filtration rate, the higher the serum uric acid. Severe stage 3 and severe stage 4 kidney damage correlate best with the increase in uric acid. Also, creatinine per se does not correlate with the level of the ejection fraction compared to the filtration rate in patients with cardiac insufficiency.
- Patients with mrHF represent a gray area, with some results discordant to the extremes of the ejection fraction spectrum
- The increased uric acid directly correlates with the increase in the volume of the left atrium area

- Severe kidney damage in patients with heart failure is associated with an increased risk of severe cardiovascular events
- End-stage chronic kidney disease is associated with the reduction of the ejection fraction and predicts major cardiovascular events
- Tissue doppler better assesses the risk of cardiovascular events in patients with severe kidney disease
- Severe diastolic dysfunction, type 2 and type 3, is associated with severe cardiovascular events.

Future research should continue in the direction of the prospective evaluation of patients with heart damage and the stratification of patients at risk, especially those patients who are in the gray area of mrHF heart failure, because these patients are at the highest risk of not being classified as potential individuals at high risk.

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The important problem remaining is how uric acid can be introduced into risk calculation scores of major cardiovascular events in heart failure, there still being multiple situations where it grows outside of heart failure, but which can provide false negative results. Also, the association with chronic kidney disease, especially in the category of patients with advanced renal impairment, uric acid can be both a cause and an effect of cardiovascular events.

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I consider that my personal contribution is a better characterization of patients with heart failure that have hyperuricemia and are at a greater risk than the general population, hyperuricemia in these patients being both a marker for the severity of cardiac disease, but also a marker for continuous damage at cellular level, with accelerating deleterious physiopathological mechanisms.

As such, patients with heart failure and hyperuricemia should be more closely followed, as they can be considered ticking time bombs and with a greter risk for decompensating heart failure, especially when these patients have several comorbid disease and are suffering from a low quality of life