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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Plasmatic NT-proBNP concentrations in patients with coexistent periodontal disease and congestive heart failure: pilot studies

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Abstract

Background: The presented pilot study was conducted in order to evaluate dynamic fluctuations of blood inflammation markers among patients with congestive heart failure (CHF) and coexistent periodontitis (PD).

Aim: The study hypothesis stated that elimination of chronic inflammation caused by PD has a significant impact on inflammation markers and, secondarily, also on the course and prognosis of CHF. N-terminal pro-B-type natriuretic peptide (NT-proBNP) and tumour necrosis factor alpha (TNF-α) markers were assessed due to their proven diagnostic significance.

Methods: Blood samples were collected at the time of CHF patients' admission to the clinical ward (I examination) and then after 3–9 months (average six months) after periodontal treatment completion (II examination). With antibiotic cover, basic periodontal parameters (such as CAL, PD, PI, BOP) were evaluated, scaling and root-planning were performed, and orthopantomogram X-rays were conducted. Patients received instructions about domestic oral hygiene procedures. Measurements were repeated during a second examination of blood samples. Obtained results were compared and statistically analysed.

Results: The initial outcome of the study confirmed the hypothesis that maintaining good and complex oral hygiene has an essential impact on blood concentration of NT-proBNP and TNF-α markers.

Conclusions: Exploration of possibilities considering medical help and treatment optimisation seems to be evident also according to improvement of prognosis, therapy effectiveness, and patient comfort. Foregoing conclusions about biomarkers are, according to authors' best knowledge, the first such results reported in medical literature.

Key words: NT-proBNP, congestive heart failure, periodontal disease, inflammatory response

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INTRODUCTION

Congestive heart failure (CHF) is a clinical syndrome, most commonly with a coronary and/or hypertension-related aetiology. This condition is linked to a high morbidity and mortality. Due to the ageing population and the increasing morbidity of coronary heart disease and arterial hypertension, which according to Framingham's study are the most common causes of CHF, early and effective treatment of heart failure (HF) is becoming increasingly important [1–7].

Congestive heart failure morbidity has been increasing in recent decades, especially within the older population, specifically patients above 65 years of age. In the United States, around 6–10% of the population are diagnosed with CHF, accounting for around 20 million patients. A similar number

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of patients have asymptomatic myocardial damage, and they will develop symptomatic HF within next five years. Currently, it is estimated that in Poland there are over 10 million patients diagnosed with CHF. The average age of patients with CHF in Europe is 74 years. It has to be noted that, despite the further development in cardiology and cardiac surgery, the increasing longevity of the population will lead to an increased prevalence of HF cases over time [8–12].

Neurohormonal activation is a very important element in the pathophysiology of CHF. It manifests itself as increased plasmatic concentrations of natriuretic peptides, which have diagnostic and prognostic properties in CHF. The essential natriuretic peptide, with a recognised role in both diagnosis and treatment monitoring of CHF patients, is the plasmatic concentration of N-terminal pro-B-type natriuretic peptide (NT-proBNP) [5, 7, 8, 13–16].

In the advanced stages of CHF it is common to observe aggravations and hospitalisations originating from haemodynamic dysregulation. This dysregulation frequently coexists with local or systemic inflammatory processes. There is a correlation between the intensity of inflammatory processes, determined by plasma concentrations of inflammatory markers, and the clinical status of patients with CHF, including their disease prognosis. Many researchers, including Japanese scientists, have shown that eliminating inflammation in the course of periodontal disease (PD) leads to a significant decrease in the plasma concentration of tumour necrosis factor alpha (TNF-α) [7, 8, 17–20]. Therefore, it could be suggested that the elimination of chronic inflammation related to active inflammation processes taking place in the periodontium, might lead to further benefits in the form of improved endothelial function of blood vessels. The subject of this pilot study was to examine the reduction of chronic inflammation related to PD influence on the clinical course and prognosis of CHF, based on the assessment of plasma concentrations of the inflammatory and neurohormonal markers NT-proBNP and TNF-α [21–29].

METHODS

Study group

The pilot study group comprised 39 patients diagnosed with chronic CHF, aged 56–88 years, including six women and 33 men (average age 62 years) admitted to the First Department of Cardiology of the Medical University of Warsaw. All included patients were also diagnosed with periodontitis. Among these patients, 10 had a determined NT-proBNP and TNF-α plasma concentration, 19 constituted a control group where NT-proBNP concentration was determined, and the remaining 10 formed an additional control group where TNF-α concentration was determined. The pilot study was conducted in accordance with ethical principles of the Declaration of Helsinki (1964) and was approved by the Bioethics Committee of the Medical University of Warsaw (decision number: KB/54/A/2013). All patients signed declarations of informed consent for participation in the study.

Diagnostic measurements

The CHF patients who qualified for the study were subjected to the following diagnostic measurements:

- biochemical examination at the moment of admission and approximately six months after periodontal treatment:
- blood morphology;
- ionogram (iodine and potassium concentration);
- lipid profile;
- determination of C-reactive protein and TNF-α concentrations;
- NT-proBNP concentration;
- fibrinogen concentration.

Evaluation of the state of oral hygiene: simplified plaque index (PI) and bleeding on probing index (BOP) when qualified for basic periodontal treatment (scaling, root-planning, sanitation of oral cavity, pathologies of oral mucosa).

The condition and number of impacted teeth, gangrenous roots, applied dental restorations, and medical needs regarding dental surgery and prosthodontics. Diagnostic tests of periodontal measurements were repeated approximately six months (3–9 months) after treatment.

Periodontal test of clinical attachment loss (CAL) with utilisation of periodontal probe type WHO 421 and orthopantomogram (OPG) dental X-ray in patients with CHF who qualified for the basic therapeutic treatment.

Based on the obtained data, a professional periodontal treatment was adopted for patients with coexisting CHF and PD at a highly specialised clinical centre. The correlation between biochemical tests of inflammatory markers (NT-proBNP and TNF-α) and the level of advancement of periodontal markers was subjected to statistical analysis.

Blood samples from all 39 patients were collected when admitted to the clinic (examination I) and 3–9 months (average six months) after the conclusion of PD treatment (examination II). Blood samples underwent separation and the obtained serum was subjected to screening in order to determine the concentration of plasma inflammatory markers. The examination was conducted with the use of a kit currently available on the market (R & D Systems, Inc., Minneapolis, USA), in accordance with the manufacturer's instructions. The whole procedure took place at the Central Laboratory of Haematology, Oncology, and Internal Diseases Clinic at the Medical University of Warsaw.

Periodontal testing was conducted in the Department of Oral Medicine and Periodontal Diseases, the Medical University of Warsaw, with the use of a periodontal probe type WHO 621. During the qualification, after applying the recommended antibiotic shield, the PI and BOP were determined, scaling and root-planning were performed, OPG

Table 1. The periodontal and oral mucosa condition — examination I

Sex	Plaque index (PI)	Bleeding on probing index (BOP)	Nicotine addiction	Pathologies in oral mucosa	Pocket depth	Clinical attachment loss (CAL)
Women	83% (5/6)	100% (6/6)	33% (2/6)	33% (2/6)	av. 2.91 mm	av. 4.11 mm
Men	81% (27/33)	90% (30/33)	24% (8/33)	18% (6/33)	av. 2.36 mm	av. 5.8 mm

av. — average

X-rays were obtained, and instructions on daily oral hygiene were provided to patients.

After the qualification was concluded, additional tests with an antibiotic shield were conducted, including the CAL measurement, evaluation of periodontal pocket depth, level of root furcation, and the degree of tooth mobility according to the three-degree scale. These measurements were recorded for all teeth, and average values were determined for each patient.

In order to increase the reliability of the findings, identical data profiles were collected in the reference groups comprising 19 patients tested for NT-proBNP and 10 patients screened for TNF-α.

Statistical analysis of test results

The results collected were subjected to statistical analysis in order to verify the extent to which the treatment influenced changes in NT-proBNP and/or TNF-α parameters. Two hypotheses were formulated and tested with the statistical protocols:

1. The difference in the decrease of value of NT-proBNP/ /TNF-α in the test group is significantly lower than the decrease of value in the reference group;
2. NT-proBNP/TNF-α values in the second measurement for tested groups are significantly lower than the values in the first measurements in both groups.

In both cases the Mann-Whitney test was used in dependent samples to evaluate the difference between measurements and in independent samples to evaluate the difference between the reference group and the test group (Mann and Whitney, 1947). This particular statistical test was implemented due to its suitability for the data set and the strength of its statistical properties, including the fact that it is unaffected by data distribution.

RESULTS

All patients were diagnosed with chronic systemic acute periodontitis according to the classification system of the American Academy of Periodontology (2000).

The pilot study, comprising 39 patients with CHF and coexistent PD, found that the average PI and BOP values were very high: the PI was 83% in women and 81% in men, and the BOP was 100% in women and 90% in men. The average depth of the periodontal pockets for women was 2.91 mm and 2.36 mm for men. The average level of clinical tissue attachment loss was 4.11 mm for women and 5.8 mm for men (Table 1).

The tests showed an increased plasma concentration of NT-proBNP and TNF-α in all of the patients at baseline (examination I) compared to follow-up (examination II). The decline rate of the values was statistically significant (Fig. 1). Maximum concentrations of NT-proBNP were detected in the first test, with a subsequent decrease in values during the six-month observation. It was observed that the average plasma concentrations of NT-proBNP and TNF-α in patients changed rapidly and significantly, with a statistically significant decline between examination I and examination II.

During the six-month-long observation, there was no aggravation of HF in any patient, and the pharmacotherapy, compliant with existing guidelines, was not modified with regard to the type or dose of medications.

Test comparing the significance of the decrease in NT-proBNP values in the test and reference groups

In the test group, the average relative change of the NT-proBNP marker was 70.29%, when comparing follow-up and baseline measurements. This corresponds to a decrease in NT-proBNP by approximately 29.71%. In the reference group, a statistically insignificant increase in NT-proBNP (–0.84%) was observed. This corresponds to a decrease in NT-proBNP of 30.55%. Figures 1 and 2 present the change of NT-proBNP concentrations in the test group and the reference group, respectively.

Statistical testing showed a significant difference in the decrease of NT-proBNP values in the test group, when compared to the reference group.

Visual analysis of the graphs presents a clear difference between both groups in the study. A downward trend is clearly visible in the case of the test group, whereas the reference group depicts a symmetrical change of values, both increasing and decreasing. In order to assess whether this difference is the result of a random division of patients into the test group and the reference group, the Mann-Whitney test was implemented, providing the following results: statistical value $W = 139$, $p = 0.0222738$.

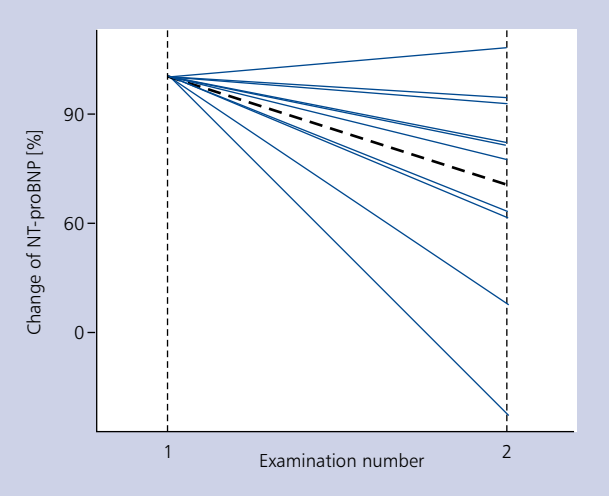

Figure 1. Relative change of N-terminal pro-B-type natriuretic peptide (NT-proBNP) values between the first and second measurements in the test group. The colours signify values of specific patients. The average value of decrease between the first and second examinations is illustrated by the dotted line

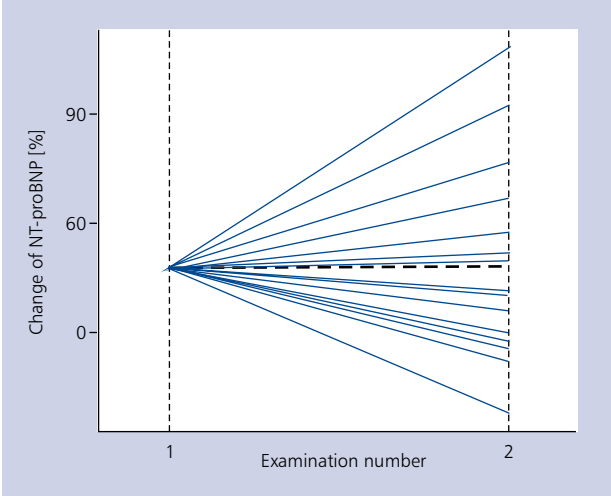

Figure 2. Relative change of N-terminal pro-B-type natriuretic peptide (NT-proBNP) values between the first and second measurements in the reference group. The colours signify values of specific patients. The average value of decrease between the first and second examinations is illustrated by the dotted line

This result negates the hypothesis that the observed difference in the decrease of plasmatic NT-proBNP concentrations between the test group and the reference group is a random result, with the statistical significance value of 0.05.

Test for the significance of the treatment impact on the change of NT-proBNP values

The aim of the second test, implemented on the basis of the examination results, was to verify whether the difference in the obtained results of measurements between the first and the second examination in the test group is statistically significant. In order to conduct this test a hypothesis was formulated, that the difference is coincidental and does not depend on the examination stage (null hypothesis). In order to probe this hypothesis, the Mann-Whitney statistical test for dependent samples was implemented. The following results were obtained: statistical value $W = 54.00$, $p = 0.0019531$.

The obtained result means that, on the level of statistical significance $p < 0.01$, we can dismiss the hypothesis that the observed difference in NT-proBNP values between examinations I and II is due to chance.

Test for the significance of the difference in the decrease of TNF-α values in the test group and the reference group

For the test group, the average relative change of the value of TNF-α marker was 28.52% between examination II and examination I. This corresponds to a decrease of 71.48%. For the reference group, an insignificant increase in the concentration of TNF-α by 2.89% was observed. The observed difference in the value of decrease between groups was therefore 68.59%.

Figures 3 and 4 show the changes in TNF-α values in the test group and the reference group, respectively.

Visual analysis of Figures 3 and 4 suggests that there is difference between the groups. A downward trend is clearly visible in the test group, whereas a symmetrical change of values both increasing and decreasing is evident in the reference group. In order to assess whether this difference is the result of a random division of patients into the test group or reference group, the Mann-Whitney test was implemented, providing the following results: statistical value $W = 100$, $p = 0.00003$.

This result negates the hypothesis that the observed difference in the decrease of TNF-α values between the test group and the reference group is a random occurrence, with a statistical significance of $p < 0.001$.

Test for the significance of the treatment impact on the change of TNF-α values

The aim of the second test, implemented on the basis of the examination results, was to verify whether the difference in the obtained values between the first and the second examination in the test groups is statistically significant. In order to conduct this test a hypothesis was formulated that the difference is coincidental and does not depend on the examination stage. In order to probe this hypothesis, the Mann-Whitney statistical test for dependent samples was implemented. The following results were obtained: statistical value $W = 55.00$, $p = 9.76562510^{-4}$.

This result suggests that the hypothesis that the observed difference between measurements for TNF-α parameters was coincidental can be negated, at a statistical level of $p < 0.001$.

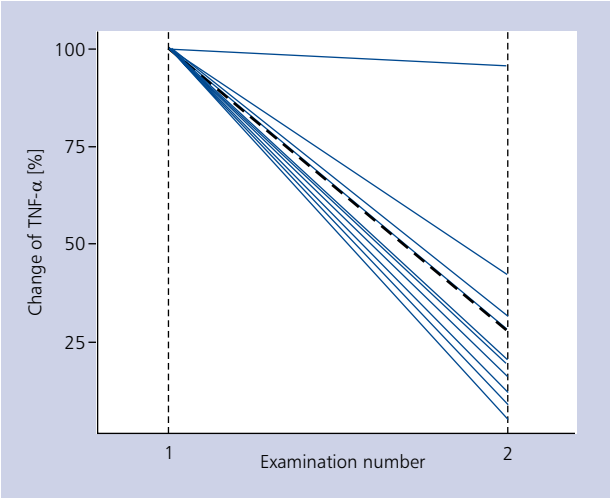

Figure 3. Relative change of tumour necrosis factor alpha (TNF-α) values between the first and second measurement in the test group. The colours signify values of specific patients. The average value of decrease between the first and second examinations is depicted by the dotted line

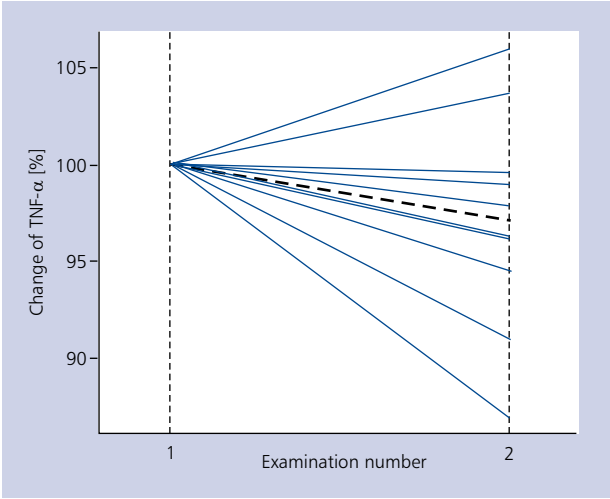

Figure 4. Relative change of tumour necrosis factor alpha (TNF-α) values between the first and second measurement in the reference group. The colours signify values of specific patients. The average value of decrease between the first and second examinations is illustrated with the dotted line

DISCUSSION

The pilot study was conducted on a group of 39 patients aged ≤ 88 years (age range 56–88 years; average 62 years) with diagnosed CHF and PD. It was noted that the NT-proBNP and TNF-α measurements recorded during admission to the ward (examination I) differed significantly from the results obtained after basic periodontal treatment (examination II). Furthermore, a statistically significant decrease in the measured values was noted during the observation period (3–9 months; average six months).

All patients were subjected to a basic periodontal treatment process comprising scaling and root planning, and potential extraction of gangrenous teeth roots (if applicable), applying the previously selected antibiotic shield. Recommended oral hygiene at home included brushing teeth twice a day, in the morning and in the evening, and rinsing the oral cavity with antiseptic agents. Patients maintained phone contact in case of any queries concerning the condition of the oral cavity. In addition to the statistically significant decline in BOP and PI values in all of the tested patients, an increase in CAL of approximately 1 mm was noted, which indicated the advantage of regenerative processes over destructive processes in the bone of alveolar outgrowths in the upper and lower jaw. A significant point is that none of the highly specialised guide bone regeneration treatments and/or guide tissue regeneration treatments were applied, highlighting the potential of including the presented procedure as a norm in CHF/PD treatment.

The authors would like to highlight the fact that the issue of correlation between PD and heart disease has been at the centre of their interest for over a decade. Previous studies, observations, and published results have concerned patients hospitalised due to acute coronary syndrome [21–23, 30, 31]. Patients treated for acute coronary syndrome in a long-term observation, of 10 or more years, will eventually be diagnosed with CHF. Thus, it seems essential to propose an optimal treatment and long-term periodontal care, which will significantly decrease secondary bacterial infection originating in the oral cavity [7, 32–35].

A two-year-long American observation, published in late 2015, concerning the introduction of bacteria from the periodontium, which are included in the "red complex", as well as *Fusobacterium nucleatum*, into the blood circulation of ApoE-null mice, found that these bacteria caused a statistically significant increase in atherosclerotic plaque volume in the descending aorta and collateral circulation vessels. The observation time was 24 months from the moment of bacterial pathogen implantation. In light of current knowledge, the formulated hypothesis increases in clarity based on these findings, fulfilling the first postulate of Robert Koch, whose detailed research methodology is still applicable [36]. Detection with the use of polymerase chain reaction also showed the presence of pathogens derived from periodontal tissue in the liver, spleen, kidneys, and lungs — organs distant from the oral cavity [35].

The results of this pilot study also highlight the problem of maintaining a sufficient and complex oral hygiene routine, which can impact the plasma concentrations of NT-proBNP and TNF-α, as shown in the present study. Individualisation and support during the implementation of oral hygiene routines in patients with CHF should be advocated in future practice. This intervention may improve the prognosis of CHF

by increasing the effectiveness of treatment and ensuring the comfort of the patient [6, 37, 38].

The results of this pilot study require confirmation based on trials in larger groups of patients. However, based on the observations of this study, it is suggested that:

— professional periodontal treatment can contribute to a decrease in the values of NT-proBNP and TNF-α concentrations in patients with coexistent CHF and PD;
— due to the fact that both of the tested markers have prognostic significance, it is likely that professional periodontal treatment of patients with CHF and PD could improve the long-term prognosis for this patient group;
— these conclusions, to the best of the knowledge of the authors, are the first such conclusions reported in the literature.

CONCLUSIONS

Scientific rationale for study: The aim of this pilot study was to evaluate the impact of chronic periodontitis treatment on the course and prognosis of patients with CHF with the use of blood markers: NT-proBNP and TNF-α.

Principal findings: The pilot study showed significant correlation between professional periodontal treatment and a decrease in the mentioned blood inflammation markers. Such treatment can improve haemodynamic effects in patients with CHF.

Practical implications: The authors suggest that patients with CHF and PD require meticulous oral hygiene, interdisciplinary holistic assessment, and treatment that can lead into improvement of life quality, medical prognosis, and neurohormonal evaluation.

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Conflict of interest: *none declared*

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Osoczowe stężenia NT-proBNP u pacjentów z niewydolnością serca i współistniejącą chorobą przyzębia: badania pilotażowe

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Streszczenie

Wstęp: W pilotażowym badaniu oceniano dynamikę zmian wybranych markerów zapalnych u pacjentów z przewlekłą niewydolnością serca (CHF) i współistniejącymi chorobami przyzębia (PD).

Cel: Hipoteza robocza zakładała, że wyeliminowanie przewlekłego stanu zapalnego związanego z PD wpływa na te markery zapalne, a wtórnie na przebieg i rokowanie w CHF. Oceniano N-końcowy propeptyd natriuretyczny typu B (NT-proBNP) i czynnik martwicy nowotworu alfa (TNF-α) mające udowodnione znaczenie rokownicze.

Metody: Do badania pobierano próbki w chwili przyjęcia na oddział, a następnie po 3–9 miesiącach (średnio 6 miesięcy) od zakończenia leczenia przewlekłego stanu zapalnego przyzębia u chorych z CHF. W osłonie antybiotykowej określano podstawowe parametry peridontologiczne związane z PD (CAL, PD, PI i BOP), wykonywano *scaling* i *root-planing*, kierowano na przeglądowe zdjęcia radiologiczne szczęk (pantomogram) oraz udzielano instruktażu dotyczącego domowej higieny jamy ustnej. Pomiary powtarzano przy drugim pobraniu krwi. Uzyskane wyniki zestawiono i przeanalizowano statystycznie.

Wyniki: Wstępne wyniki potwierdziły hipotezę, że utrzymanie właściwej, kompleksowej higieny jamy ustnej wpływa na osoczowe wartości stężenia NT-proBNP i TNF-α u chorych z CHF.

Wnioski: Poszukiwanie możliwości pomocy i optymalizacji leczenia pacjenta z CHF wydaje się być oczywiste, również w kontekście poprawy rokowania, wzrostu efektywności terapii i poczucia komfortu pacjenta. Powyższe wnioski dotyczące biomarkerów są, wg najlepszej wiedzy autorów, pierwszymi informacjami o znaczeniu leczenia PD dla chorych z CHF raportowanymi w piśmiennictwie.

Słowa kluczowe: NT-proBNP, przewlekła niewydolność serca, choroby przyzębia, odpowiedź zapalna

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