

Research Article

C-Reactive Protein (CRP) and Health Resort Reaction

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Incident tissue-damaging factors trigger a systemic response manifested by inflammatory reaction. Acute-phase proteins are a diagnostic and prognostic marker in various systemic homeostasis disorders. In the course of health resort therapy, a so-called health resort reaction is observed presenting with, e.g., exacerbation of organ-related disorders, elevated body temperature, increased erythrocyte sedimentation rate, and leukocyte counts. The objective of the study was to demonstrate a change in the concentration of C-reactive protein (CRP) as a result of health resort radon therapy as well as to determine the relationship between this change and the phenomenon known as health resort reaction. The study was conducted in Swieradow-Zdroj resort. The study population consisted of patients undergoing radon-active water bath treatment. Standard tests were used to determine CRP levels before the treatment as well as 5 and 18 days into the treatment. The study group consisted of $n = 34$ patients with osteoarthritis and spondyloarthritis. The control group consisted of 17 employees of the health resort who were also burdened with osteoarthritis or spondyloarthritis yet did not undergo radon therapy and had absolutely no contact with radon materials. The study revealed no statistically significant increase in the concentration of CRP. This trial is registered with NCT03274128. The study was carried out as part of the statutory task SUB.E060.19.001.

1. Introduction

Radon-active waters contain small quantities of an unstable radioactive element radon along with the products of its radioactive decay. If the activity of radon exceeds 74 Bq/L (2 nCi/L) and the water meets all the required utility and hygienic requirements, it may be used for therapeutic purposes. Radon is a noble gas, odorless and colorless, well-soluble in water, particularly that with low mineral or acid content. Radon is a product of radioactive decay of uranium and thorium. It exists in a variety of isotopes, with radon-222, formed directly by alpha-decay of radium-226, being predominant. The emitted alpha particles are characterized by low penetrability and high ionizing power. The half-life of radon-222 is 3.8 days. Due to the instability of the element, its levels undergo continuous fluctuation in circadian as well as seasonal patterns. Radon is also observed during treatment, particularly due to technical reasons (water being stored in reservoirs, transferred along pipelines, heated,

cooled) as well as due to the extensive use of radon-active water. The losses in the radon content may be as high as 40–80%. Due to the variability in radon levels at the water source being this high, calculation of administrated doses is impossible and therefore not carried out. [1] Radon absorption occurs in 95% via lungs. Elimination occurs mostly via lungs (90%), with the remaining amounts being eliminated through kidneys and skin.

While in the bath, patients absorb radon mainly through their respiratory tract since radon and its derivatives accumulate in large quantities above the surface of water. Radioactive precipitate settles on skin and remains there for several hours. Radioactive decay processes occurring within the body are of variable intensity, largely depending on the quantity of adipose tissue. Adrenal cortex, liver, and muscles also play an important role in the process. Anti-inflammatory, desensitizing, and analgesic effects of radon are explained by stimulation of adrenal cortex and increased production of steroid hormones (luteinizing hormone,

growth hormone, cortisol, testosterone, estradiol, and estrinol). Radioactive treatment improves peripheral circulation, reduces swelling as well as joint and musculotendinous pain, and improves motor output. Other findings include reduced arterial blood pressure, cholesterol, and triglyceride levels, reduced erythrocyte sedimentation rates, increased hemoglobin levels and erythrocyte counts, increased levels of ionized calcium, parathyroid hormone, and calcitonin, as well as increased rate of elimination of harmful metabolites [2–5].

Health resort (balneological) reaction is a systemic reaction of adaptation in response to external factors (stimuli). It is a beneficial element of health resort treatment leading to metabolic transformations of significant importance for the system. Balneological reaction is commonly a result of therapeutic stimuli exceeding the compensatory abilities of the system. It results in excessive secretion of histamine, stimulation of autonomous nervous system and endocrine glands, and secretion of adrenocortical hormones. These changes result in increased immunity and intensity of regenerative reactions. The mechanism of balneological reactions has not been fully elucidated by research studies. However, it is assumed that the reaction to the stimulus occurs mainly within the autonomous nervous system. The intensity of health resort reaction depends on the type and quantity of natural therapeutic materials used in the treatment, in this case the radon-active waters. Other factors that determine the intensity of the reaction are the age and overall health of patients. Clinical presentation of the reaction may include specific symptoms varying as depending on a particular disorder as well as nonspecific symptoms associated with the systemic responsiveness to the therapeutic stimuli. Most commonly, these include symptoms hitherto not observed in the patient. The symptoms may be of generalized as well as localized character; their intensity may also vary. Systemic symptoms include increased erythrocyte sedimentation rates and leukocyte counts, elevated body temperature and arterial blood pressure, myalgia, and a drop in overall fitness level.

Local symptoms include mainly skin reactions such as erythema, itching, and hives. The reaction may occur in as many as 70–80% of health resort patients. The onset of health resort reaction is most commonly observed on days 2–4 of the resort treatment, while the intensity of the reaction peaks on about day 7. Starting from about day 14, the symptoms of health resort reaction start to resolve. Exacerbation of the primary disease and activation of inflammatory reactions are often observed during the reaction. Clinical symptoms of the health resort reaction include intensification of myalgia and arthralgia, headaches, angina, joint swelling, reduced appetite, fatigue, irritation, malaise, and sleep disorders. A characteristic feature of the health resort reaction is its multistage course including: phase I—initial—lasting from day 2 to day 7—labile reactions; phase II—ergotropic—lasting about 1 week—increased intensity of reactions; and phase III—trophotropic—resolution of the reaction; the reaction is followed by the recovery and adaptation period lasting until the completion of the treatment. In phase III, clinical improvement is achieved and

experienced by patients for 8–10 months after returning home. Health resort reactions are observed most commonly in patients taking sulfur or radon baths as well as comprehensive peat treatments. In the period of intense reaction symptoms, the intensity of therapeutic stimuli should be reduced or the treatment should be temporarily discontinued [6–8].

C-reactive protein (CRP) belongs to a heterogeneous group of proteins synthesized in the liver [9]. Concentrations of CRP change during acute and chronic inflammatory conditions [10]. Biological properties of CRP include complement activation, stimulation of phagocytosis, and protective activity upon autoimmunization with auto-antigens [11]. CRP is deposited at damaged tissue sites where it induces complement activation or macrophage attraction [11]. CRP may also transport tissue materials released in necrotic processes to other sites within the system [11]. Due to these properties, CRP is not only a marker, but also an active element of the inflammatory process, its main function being the binding and detoxification of specific biological materials [12]. CRP is considered to be the only active-phase protein that meets (albeit to a limited extent) the diagnostic requirements, and may be used in certain cases for the detection of infections, prediction of disease progression, and monitoring of treatment responses [13]. In recent years, potential use in the diagnostics and prevention of cardiovascular diseases, type II diabetes, and Crohn's disease was also suggested. According to Koj, CRP continues to be the subject of research in various diagnostic applications [12, 13]. The objective of the study was to demonstrate a change in the concentration of C-reactive protein (CRP) as the result of health resort radon therapy as well as to determine the relationship between this change and the phenomenon known as health resort reaction.

2. Materials and Methods

The study was conducted in Swieradow-Zdroj resort based on the clinical trial number NCT03274128 as part of the Polish Radon project with the registration number of the Department of Science of the UM KLASZTER-3/2014. Observation was carried out in patients undergoing resort treatment for the period of 21 days. Venous blood was collected from patients before the treatment as well as 5 and 18 days into the treatment. Heparinized plasma was used for CRP determinations. Diagnostic CRP determination is achieved by means of immunological latex turbidimetry. In the first step of the determination procedure, the test sample is mixed with a suspension of latex-bound monoclonal mouse antibodies against human CRP. In the next step, CRP molecules bind the antibody-latex particles resulting in agglutination and increased turbidity of the sample. Determination of CRP is achieved by the measurement of the dispersion of light due to the turbidity. The degree of turbidity is measured as a change in the absorbance. The measurement is carried out at the wavelength of $\lambda = 630$ nm. The change in the absorbance is directly proportional to the CRP content in the sample [14]. Physiological CRP levels are not higher than 5 mg/L; levels higher than 10 mg/L are

considered pathological. Further increase in CRP levels may be dramatic and reach up to 1000 times the baseline value within 24–48 hours from the onset of the triggering factor.

The study was carried out according to a nonrandomized design. The study group consisted of $n = 34$ patients with joint or spinal pain due to osteoarthritis or discopathy. The age range was 47–63 years, with the mean age of 56.5 years. The group consisted of 23 female and 11 male patients. The selection criteria included the established diagnosis of osteoarthritis and/or spondyloarthritis, age in the range of 45–65 years, consent to participate in the study, and lack of contraindications for comprehensive health resort treatment. Exclusion criteria included the lack of consent for participation in the study, age below 45 or above 65 years, presence of disorders constituting contraindications for the treatment (according to the standard list of indications and contraindications for health resort treatment) as well as the presence of metabolic disorders. Therapeutic radon-active water was used in the treatment. Treatment measures included whole-body immersion radon baths—temperature 37°C, duration 15 min.—administered every second day, and oral inhalations of radon—temperature 37°C, duration 15 min.—administered every second day. Baths and inhalations were administered in an alternating fashion—patients received a total of 15 radon administrations during their resort stay period. In addition, the treatment included kinesiotherapy (30–45 min) and physical therapy (extent limited due to the possibility of immune system activation). The study treatment took advantage of radon-active waters of the Świeradów-Zdrój health resort, which have been used for therapeutic purposes for more than one hundred years. The waters are characterized by low mineral content, and their main therapeutic factor consists in their radon activity of 303.1–441.5 Bq/L. Alpha radiation measured within the treatment facilities (inhalatorium, bath cabins, and pool) was in the range of 184.4–450.0 MeV. The measurement permits evaluation of patients' exposure. The dose of absorbed radiation was not determined since the radioactivity was a variable parameter. It depended on body composition, particularly on the contents of adipose tissue and absorption area, concomitant diseases, as well as to operational radiation losses as described in the introduction. Measurements within the treatment facilities were taken daily using certified detectors. Every 3 months, the measurement results are analyzed at the Department of Radiological Protection of the Nofer Institute of Occupational in Lodz.

A control group was also provided for in the study design. It consisted of 17 individuals selected from among the resort personnel and included 10 female and 7 male subjects aged 50 to 62 years, with the mean age of 54.2 years. Subjects enrolled to the control group were also burdened by osteoarthritis of the motor organs while not taking advantage of the treatment facilities of the resort (i.e. not exposed to radon). The main selection criteria included the established diagnosis of osteoarthritis and/or spondyloarthritis, age in the range of 45–65 years, consent to participate in the study, and lack of contraindications for treatment. The inclusion and exclusion criteria in the control group were

the same as in the study group. Symptoms typical for balneological reactions were observed in the study group subjects, while the subjects in the control group reported no complaints of any kind.

The study received an approval from the Bioethics Committee of the Wrocław Medical University—opinion no. 135/2015, and a written approval of the Head of the Świeradów-Czerniawa health resort. Individual written consents in line with the sample consent recommended by the Bioethics Committee of the Wrocław Medical University were obtained from all patients.

Statistical analyses were carried out using the Statistica 13 software package (StatSoft, Inc., USA). Arithmetic means, medians, standard deviations, and variability ranges (extreme values) were calculated for measurable variables. All quantitative variables were tested for the type of distribution using the Shapiro-Wilk's test. Results obtained in the study and the control group were compared using the Mann-Whitney U test. In-group comparisons of results obtained in measurements I, II, and III were carried out by means of unifactorial analysis of variance (ANOVA). The significance level for all comparisons was established at $\alpha = 0.05$; the p values were rounded to 4 decimal places.

3. Results

Table 1 lists the CRP levels as measured in the study group and the control group. Figures 1 and 2 present in-group comparisons of the results of measurements I, II, and III, while Figures 3–5 present the comparisons of the results of individual measurements between the study group and the control group.

4. Discussion

In the study group, CRP concentrations observed in each of the three measurements were within the normal limits. Changes observed in the comparison of mean and median CRP concentrations as determined in measurements I, II, and III turned out to be statistically nonsignificant ($p = 0.1102$) (Figure 1). Therefore, one may conclude that during the critical health resort reaction onset period, CRP concentration was subject to a slight change and did not go beyond the limits of the normal range. Also, in the control group, the changes in CRP levels as determined in measurements I, II, and III were also within the normal limits. Statistical analysis revealed that the CRP level changes in this group were at the borderline of statistical significance ($p = 0.0529$) (Figure 2). However, fluctuations in CRP concentrations did not go beyond the limits of the normal range and were clinically insignificant. Importantly, no symptoms of health resort reactions were observed in the control group as opposed to the study group. Differences in the results between the study group and the control group as determined in measurements I and III were not clinically significant (Figures 3 and 5). A significant difference at the level of $p = 0.0502$ was demonstrated for measurement II (Figure 4); however, this was of no importance for the overall premises since the subjects in the study group did not

TABLE 1: CRP concentrations in mg/L—statistical analysis—study and control groups.

Variable	Group	Valid <i>N</i>	Mean	Median	Minimum	Maximum	Lower quartile	Upper quartile	Std. Dev.
Measurement I	Study	34	1.91	1.43	0.21	6.28	0.77	2.5	1.91 ± 1.59
Measurement II	Study	34	1.73	1.6	0.11	6.20	0.53	2.52	1.73 ± 1.43
Measurement III	Study	34	1.78	1.61	0.15	8.59	0.52	2.43	1.78 ± 1.68
Measurement I	Control	17	4.06	2.12	0.37	25.09	1.18	3.19	4.06 ± 6.28
Measurement II	Control	17	2.98	2.74	0.37	9.15	0.99	4.14	2.98 ± 2.47
Measurement III	Control	17	2.08	1.67	0.29	7.41	1.31	2.2	2.08 ± 1.67

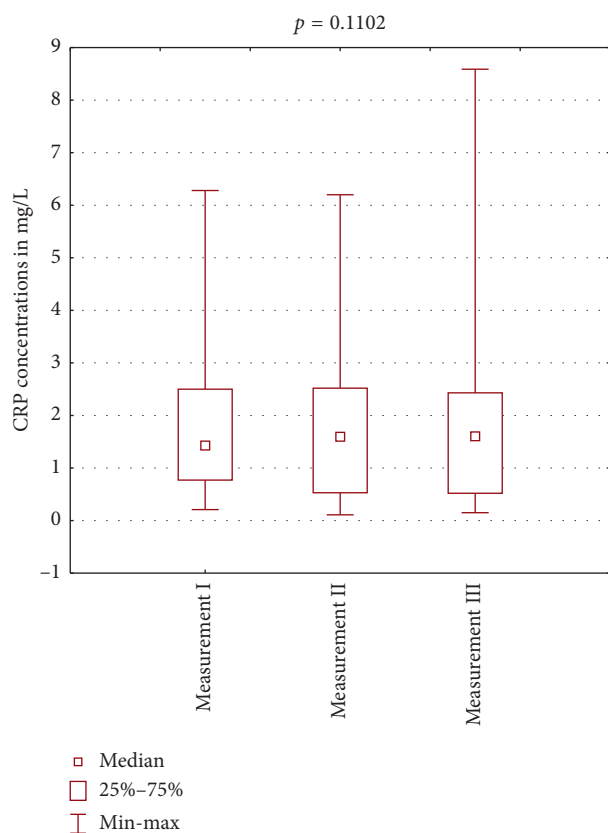


FIGURE 1: In-group comparisons of the results of measurements I, II, and III—the study group.

undergo any treatment. The absence of any significant changes in CRP levels was also confirmed in the study by Franke et al. [15] Contradictory results were presented by Oláh et al., who demonstrated a statistically significant and persistent (3 months after a cycle of balneological treatment) reduction in the CRP levels in patients undergoing medicinal thermal bath treatment [16].

The health resort reaction as a specific systemic response finally leading to an improvement in patients' condition in the last phase of health resort treatment is probably a manifestation of a controlled disturbance in systemic homeostasis due to the comprehensive effect of stimulatory treatment being administered over a period of 10 days [17].

The health resort reaction is an important indicator of systemic response to the therapeutic stimuli in the course of health resort treatment [18]. Evaluation of the study results warrants the assumption that human body reacts to a balneological stimulus as a factor that initiates biochemical,

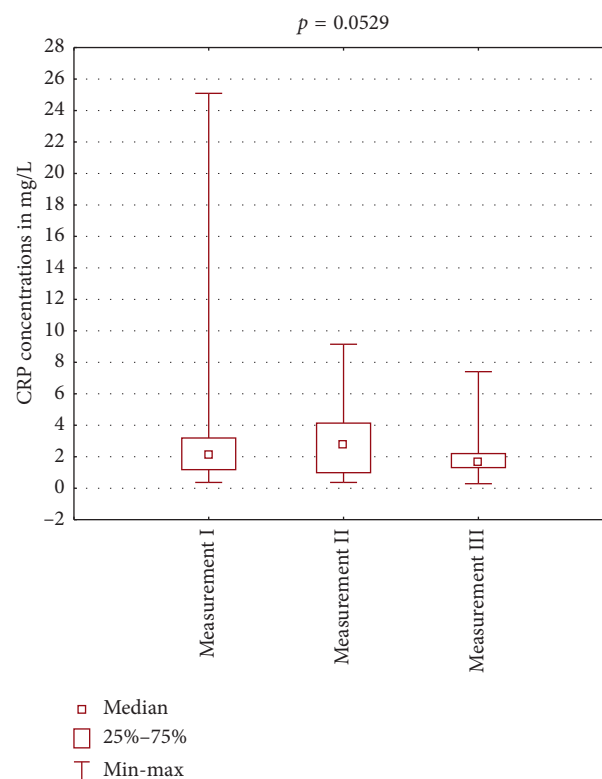


FIGURE 2: In-group comparisons of the results of measurements I, II, and III—the control group.

cellular, metabolic, immunological, and hormonal reactions [19–23], presumably involving free radicals. [24] These reactions give rise to the manifestation of various symptoms and complaints. Further on, the accumulation of stimuli results in metabolic retuning and initiation of defense mechanisms as demonstrated by Rühle et al. [25]. The final outcome consists in initiation of adaptation and regenerative processes leading to an improvement in clinical condition after the completion of treatment [26, 27]. The health resort reaction is the subject of clinical assessment only as a systemic phenomenon, with no diagnostic methods to determine the dynamics of the condition being available to date.

No precise mechanism for the development of health resort reaction was determined in scientific research. As a systemic condition secondary to the balneological stimulus, health resort reaction is an important marker of the efficacy of health resort treatment. At low intensity, it is a positive prognostic marker of treatment efficacy. Too high intensity of the reaction may be indicative of a significant deterioration of patient's health. Determination of diagnostic

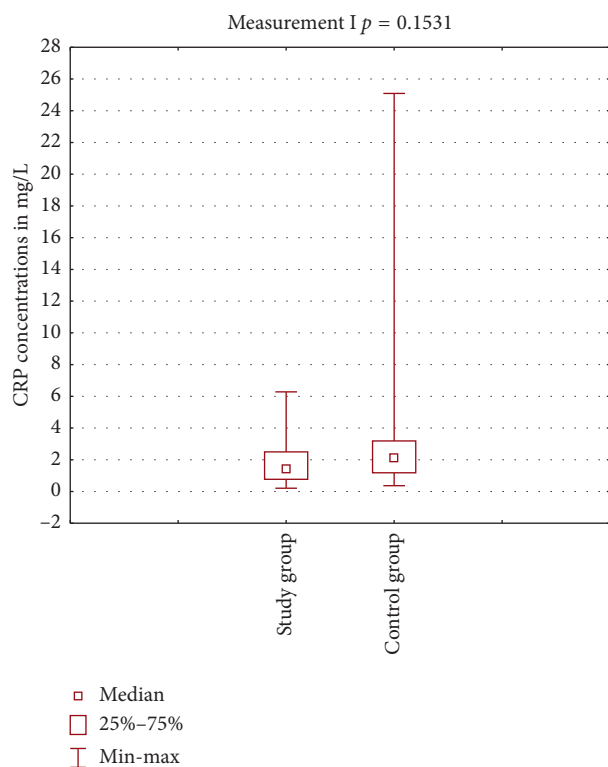


FIGURE 3: Analysis of the results of measurements in both groups—measurement I.

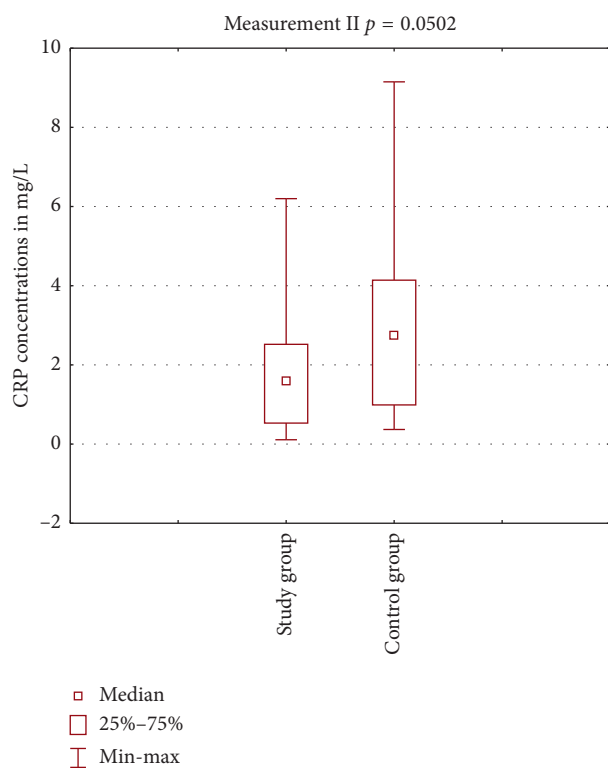


FIGURE 4: Analysis of the results of measurements in both groups—measurement II.

markers facilitating the assessment of the activity of the health resort reaction and the ability to diagnose and prevent overly strong reactions are important issues. Acute-phase

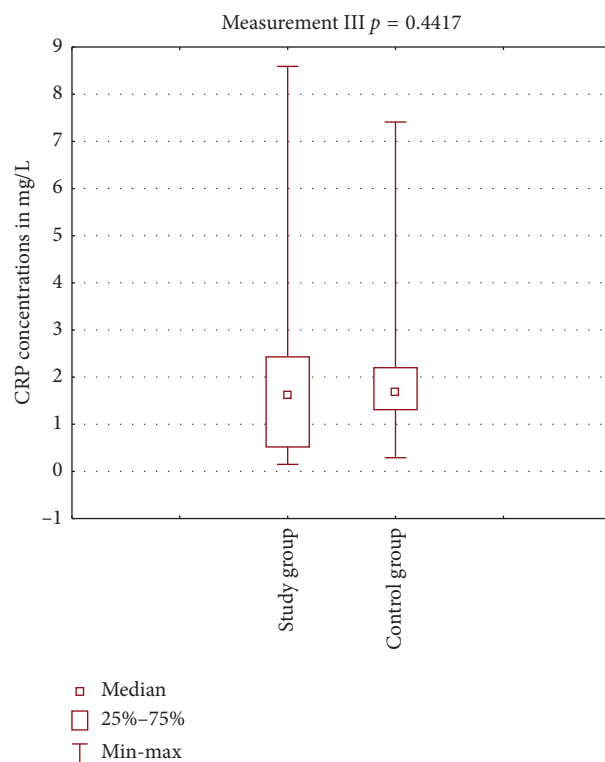


FIGURE 5: Analysis of the results of measurements in both groups—measurement III.

proteins, and particularly the CRP, raised some hopes in this respect. As part of this study, an attempt was made at assessing the potential of CRP as a marker for use in the assessment of the dynamics of the health resort reaction. Unfortunately, CRP levels turned out to be useless in this assessment. Numerous studies were conducted to date in health resort medicine to assess the changes in CRP levels in response to various balneological stimuli. Misztela et al. demonstrated that artificial sulfur baths led to a statistically nonsignificant drop in CRP levels in health resort patients, while the main observation consisted in clinical improvement [28]. Ponikowska et al. demonstrated the effect of peat treatment, e.g., on CRP levels [29].

Numerous authors point to the role of cytokines in the induced expression of acute-phase proteins while highlighting their importance for clinical diagnostics. The role of C-reactive protein being a marker of numerous pathological conditions is the subject of a particularly detailed analysis. Its binding and detoxification of biological materials leads, e.g., to bacterial agglutination and elimination of infection [30]. In the case of health resort reaction, despite various clinical symptoms resembling those of an inflammation, the system does not fight any foreign biological material.

The C-reactive protein (CRP) is probably the best, despite nonspecific biochemical marker of pathological processes, mainly those of inflammatory character. Thanks to its high speed and relatively low cost, determination of CRP levels provides a fast method for the diagnosis and the assessment of the stage, the extent, and the dynamics of changes of pathological condition [31, 32].

CRP is the most frequently determined acute-phase protein. It is one of the relatively sensitive diagnostic and prognostic markers for inflammatory disorders, infections, cancers, hepatitis, pancreatitis, vascular diseases, atherosclerosis, and other systemic homeostasis disorders [33]. The key effect of acute-phase proteins consists in restoration of systemic homeostasis by means of activation of nonspecific reaction to reduce the tissue damage caused by bacteria and lysosomal enzymes from phagocytic cells as well as the increased chemotactic activity [34]. Studies to assess the applicability of CRP as a marker in various disorders are continuously under way. Recent years brought about the information on attempted application of acute-phase proteins in the diagnostics of schizophrenia, alcohol-related liver damage, or genetic diseases [35].

As mentioned in the introduction, CRP is not only a marker, but also an active participant in the inflammatory process; therefore, the lack of changes in acute-phase protein levels as observed in the study is assumed to be due to the lack of foreign material. High-intensity balneological stimuli that would lead to tissue damage would lead to higher changes in CRP levels. These, however, would constitute adverse and unwelcome effects. Each procedure has its specific duration and dosage, and the health resort therapy is obviously aimed at activation rather than destruction of tissues. Complications of health resort therapy, particularly those involving an excessive health resort reaction, are examples of such adverse and unwelcome effects. Such complications are most commonly due to the nonadjustment of treatment to the adaptation capacity of patients' bodies as well as to patients' noncompliance (longer-than-recommended times spent in the baths, systemic overheating, and skipping recommended rest periods after taxing procedures).

To sum up, the relationship between CRP and the health resort reaction continues to be the subject of research studies and requires further observation.

5. Conclusion

CRP as a nonspecific biochemical marker of pathological processes of mostly inflammatory character should not be used in the assessment of the dynamics of health resort reaction.

Data Availability

All data are contained and described within the manuscript. The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors report no conflicts of interest in this work.

Authors' Contributions

J. K. L. and M. P. B. contributed equally to this article, made substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data; M. K. and J. K. L. involved in drafting the manuscript; M. K., J. K.

L., and MS involved in data acquisition; M. P. B. and J. G. revised it critically for important intellectual content and gave final approval of the version. All authors read and approved the final manuscript.

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