Introduction

According to WHO [1, 2] cardiovascular diseases are the most common conditions leading to death. Every third adult in the world suffer from arterial hypertension (AH). It is one of the reasons of stroke, heart attack and other cardiovascular outcomes in 50% of cases leading to death. But the total mortality rate is even higher if we take into account impaired microcirculation, rheological and biochemistry properties of blood that provoke the development of neurological, pulmonary, nephrological and oncological diseases. In addition, blood delivers immune cells to the places of pathological processes, so the development and practical application of different methods of treatment and prevention of the hematological diseases is one of the major problems of modern healthcare.

It is impossible to solve any problem in medicine without understanding the mechanisms under the development and evolution of biological systems. Internal biological rhythm regulate and synchronize of the activity of all physiological processes by nervous and humoral systems [3]. On the one hand the nervous system is autonomous and it work through the complex arrangement of neurons. Humoral regulation, on the contrary, is strictly dependent on endocrine tissues synthesizing hormones and on their delivery via the vascular system to target tissues.

In addition to the regulatory function, the cardiovascular system performs a transport function: red blood cells transfer oxygen to tissues and plasma ensures the delivery of immunocompetent cells and nutrients to various organs [4].

Any biochemical blood disorders can lead in the future to hemodynamic impairment, which already leads to local pathologies and the development of diseases of organs and systems.

For example:

Decline in oxygen and nutrition supply of pancreatic islets of Langerhans leads to impaired insulin synthesis, that increase the risk of diabetes.

Decline in oxygen and nutrition supply of hepatocyte leads to an impaired function of liver that causes the manifestation of toxic complications, as well as the development of non-infectious hepatitis.

Impaired delivery of immune cells to target tissues is an independent factor that promotes carcinogenesis.

Decreased utilization of metabolic products and toxins can cause severe intoxication and cell dysfunction in affected organs and tissues.

Therefore, every intervention leading to the prevention of cellular pathologies of the blood helps to prevent the occurrence of many diseases and increase life expectancy. Drug therapy, physical, chemical methods or with the help of laser energy of the corresponding wavelengths could be helpful. The main is not to choose the method, but to achieve a properly selected systemic effect. Nowadays the most effective and less invasive techniques are of the greatest relevance. Transcutaneous laser blood irradiation (TLBI) is one of that methods. The compact size, the optimal irradiation zone with proper therapeutic effect and the safety make it possible to consider TLBI as a new topical and effective approach in the field of laser therapy. The purpose of this review is to describe methods of treatment and prevention by TLBI using a low-power laser diode with a wavelength of up to 950 nm, since the range from 600 to 950 nm is considered as the most effective effect on the tissues, as well as comparing the modern method with stationary earlier analogue - intravenous laser blood irradiation (ILBI) [5].

Efficiency and features of low level laser blood therapy

Despite the lack of a widespread use of Low level laser therapy (LLLT) is still at the stage of implementation in healthcare, so it is not in a widespread use in medicine. Nowadays there are a lot of the ongoing systematic meta-analyzes evaluating the effectiveness of lasers in the treatment of hematological, endocrine, neurological and dermatological diseases. So there is a fairly clear tendency to consider LLLT as a completely new, safe, effective and cost effective method of the treatment and prevention of diseases.

LLLT can easily compete with pharmacological therapy in the treatment and prevention of certain diseases as more effective. This is especially true for hematological diseases [6].

Laser blood irradiation (LBI) as one of the ways to use low level laser radiation in medicine existed for more than 30 years. At the same time, thanks to the use of modern emitters, modern devices take into account the physiological characteristics of the skin and subcutaneous fat, which have the ability to absorb and retain light. This approach allows you to achieve maximum efficiency, minimize the size of devices and simplify the use of LBI. [7]

It is worth noting that until recently, LLLT could only be performed in the presence of the physician as it was invasive intervention, because of the catheterization of peripheral veins, so it was called intravenous laser blood irradiation (ILBI) [8]. But with the development of technology today it is already possible to carry out LBI on an outpatient basis and non-invasively. Thus, this new approach prevents the development of infections and any other complications associated with peripheral vein catheterization.

In a recent study by Momenzadeh S. et al. A comparison was made of the efficacy of ILBI and TLBI in the treatment of myofascial shoulder syndrome. According to the results there was an improvement in the quality of life and a decrease in pain intensity in the ILBI and TLBI groups in comparison with the placebo group, while the difference in effectiveness between this two approaches was not significant. [9] However, TLBI is a method of choice as non-invasive and because it eliminates the complexity of the procedure, especially in patients with vascular diseases.

The study of hematological parameters after LBI

Experimental studies of LBI revealed significant changes in the morphological structure of peripheral blood based on the effect of TLBI. There was reticulocytosis after therapy with a slight increase in the number of red blood cells with a sequential increase in resistance. [10]

Even after one session there was an increase in the number of neutrophils in the blood smear (up to 192%), eosinocytes (up to 111%), basophils (up to 80%), lymphocytes (up to 19%). These results were recorded for one hour after therapy with a simultaneous decrease in the number of monocytes and segmented neutrophils to 62 and 19%, respectively. The authors associated an increase in neutrophils with stimulation of leukopoiesis. An increase in the number of lymphocytes and basophils was associated with the migration of mature cells from the sinus of the bone marrow, spleen, and pulmonary vessels. The decrease in the number of monocytes and segmented neutrophils was explained by their accelerated migration into the tissue from the bloodstream. Similar changes in the morphology of the blood can be observed when an individual target organ is irradiated in an animal model. The effect of prolonged laser irradiation on the body caused an ambiguous reaction of white blood cells: from leukopenia after single-phase irradiation to persistent leukocytosis after multiphase irradiation.

Thus, in case of change of total rate of WBC there was a significant fluctuations in the shape of leukocytes: stable lymphocytosis and a sharp decrease in amount of segmented leukocytes that became more stable with the subsequent laser exposure [11]

The influence of LBI on the enzyme activity and lipid peroxidation

It was noted in various studies that there is a positive effect of laser therapy on lipid peroxidation (LPO) in various diseases and pathological conditions. [12] There is a significant increase in the number of enzymes, kinins and lipid oxidation products (LOPs) in the blood within 24 hours even after the first session of LLLT. Interestingly, the level of lipid peroxidation increased only in plasma, while there was a tendency to a decrease in lipid peroxidation in red blood cells.

The authors explain this phenomenon by an increase in the rate of release of biologically active substances from damaged organs and tissues. They improve blood metabolic properties and also stabilize the hemodynamics. This phenomenon was also confirmed by the results of clinical observations in which the best progress was observed in patients after laser therapy compared with the control group. During the experiments, a certain increase in the activity of catalase was also determined. The function of this enzyme is the destruction of toxic peroxides formed during various metabolic processes in the body [13].

Increased catalase activity explains the effectiveness of the use of LLLI in various inflammatory processes, reducing swelling and pain with the acceleration of the regeneration affected tissues and their functional recovery.

After LBI in addition to catalase activity, the bioenergetic activity of the main intracellular enzymes also changes. Monochromatic red light is able to increase for a short time the concentration of glucose in the blood, lower the level of pyruvic acid and increase the levels of aldolase and lactate dehydrogenase for 10-30 minutes in animal models. Some reviews report that radiation can stimulate the activity of cytochrome oxidases, catalases, and phosphatases [14].

The influence of LLLT on the serotonin concentration in patients with headache

M. Tomaz de Magalhaez et al. showed in his study the effects of LLLT on blood flow and serotonin (5-HT) and cholinesterase levels in patients with chronic headache. In this case, the levels of 5-HT and cholinesterase in whole blood were evaluated three days before, immediately after and three days after laser irradiation. The assessment of pain after treatment decreased to 5.8 points, which corresponds to a 64% reduction in pain.LLLT also leads to a slight short-term decrease in blood flow velocity. Moreover, 5-HT levels were significantly increased three days after therapy. Cholinesterase levels remained unchanged at the analyzed time points. These is a clear connection between the regulation of blood flow in the temporal artery after irradiation and also a link between the intensity of the LLLT and the level of 5-HT in patients with tension headache. According to this data LLLT could be used as one of the methods for arresting and preventing headaches. [15]

Modulation of the immune system by laser therapy

It is definitely necessary to provide further study of the mechanisms that are under the proper effects of LLLT to understand the opportunities of their further application in different areas of medicine, for example in ophthalmology. Despite this, laser therapy has been widely used in sports medicine and rehabilitation to heal wounds and restore the function of various tissues since the early 1980s.

And with a description of more precise cellular mechanisms of photobiostimulation in eukaryotic systems described in Karu et al. [16] Laser therapy has become widely used in immunology and oncology.

Waves with a length of 660 nm and 905 nm lead to a significant acceleration of lymphocyte proliferation in the presence of red blood cells [17]. Previous studies have shown that photobiostimulation of immune cells occurs by increasing the enzymatic activity on mitochondrial cysts, promoting additional ATP production, accelerating metabolism and, as a result, further differentiation of lymphocytes [18].

It is also worth to consider that such effects can be achieved only with the use of whole blood in vitro or directly in vivo, because photomodulation with a wavelength of 600-700 nm in the presence of red blood cells enhances the effect of laser radiation on the lymphocyte culture due to the optical properties of hemoglobin.

One of the possible mechanisms of that effect was demonstrated by other studies [19, 20] and confirmed by I. Stalder et al. Due to their data hemoglobin is able to catalyze the formation of free radicals in the presence of hydrogen peroxide by the Fenton reaction. Since hydrogen peroxide is present in all biological systems, including blood, when we use laser irradiation at given wavelengths in a presence of hemoglobin, it can contribute to the formation of reactive oxygen species (ROS)

This hypothesis was confirmed by a superoxide dismutase test and measurements of malondialdehyde levels reflecting the work of antioxidant protection, in which superoxide dismutase in vivo performs the function of eliminating ROS and restoring the functioning of physiological systems. An increase in the ROS concentration leads to an increase in the level of superoxide dismutase in the blood. In addition, an increase malondialdehy, a marker for the lipid peroxidation, also demonstrates a normal body response to an increased level of lipid peroxidation products [21].

Therefore, an increase in the concentration of superoxide dismutase and malondialdehyde in response to laser stimulation of the blood allows to reduce the concentration of ROS and LOPs, to stimulate the proliferation and further differentiation of cells of the human immune system. Thereby it improves the body's immune response in infectious and non-infectious chronic inflammatory diseases. One of the mechanisms of this effect is based on improvement of T-killers that help to prevent oncological processes [22].

Laser blood irradiation and diabetes

According to experts, in 2014 there were 422 million patients with diabetes mellitus [23], but already in 2018 there were more than 500 million cases of type 2 diabetes. Moreover, according to experts, a further increase in prevalence will be observed mainly in low-income countries [24].

Despite the chronic course of the disease, there is a high risk of mortality among the population, manifested mainly due to increased blood sugar. At the same time, constant hyperglycemia contributes to the rapid development of arterial hypertension (about 50% of patients), coronary heart disease (18% of patients) and diseases such as macroangiopathy of the lower extremities, diabetic sensory polyneuropathy and diabetic cataract (9, 20 and 8% respectively) [25].

The results of a 2015 meta-analysis showed that LBI significantly reduces blood glucose levels in patients with type 2 diabetes. The glucose level in the peripheral blood decreases by 14 mg / dl immediately after laser therapy. This is due to the effect of laser irradiation on arginine and an increase in the production of nitric oxide (NO). Arginine, in turn, affects the release of hormones such as glucagon, insulin, growth hormone, prolactin and catecholamines [26]. This cascade of reactions also reduces tissue hypoxia, stimulates oxygenation, and normalizes tissue metabolism. [27]

Many experts in the field of endocrinology agree that even in advanced cases of diabetes, laser irradiation of blood can contribute to a partial restoration of pancreatic function and normalize blood glucose levels. In addition, laser therapy stimulates the work of Na^+ / K^+-ATPases, Ca^{2+} and Mg^{2+}-ATPases, which activity is significantly reduced in patients with diabetes. Therefore, LBI can be used as one of the components in the treatment and prevention of diabetes mellitus and its complications. However, it is worth saying that most studies evaluating the level of glycemia in patients with diabetes have been carried out for a short period. This is why it is also necessary to carry out studies evaluating the long-term effect of TLBI in patients with diabetes mellitus to evaluate the impact of laser blood irradiation [28].

Decrease and constant control of sugar within normal limits for more than three months due to properly selected therapy can also lead to a decrease in glycated hemoglobin, which is well known as a risk factor for long-term complications of diabetes mellitus. Such a result improves the course of the disease and allows the attending physician to plan further treatment. Also, it significantly reduces the risks of complications of diabetes, including the risks of developing cardiovascular outcomes [29].

Arterial stiffness and transcutaneous laser blood irradiation

Nowadays arterial stiffness (AS) is one of the recognized markers of the development of cardiovascular diseases and mortality. The pathophysiological processes of increased AS involve many cascades of remodeling. Inflammatory, protease and oxidative shifts are the most significant pathways. At the same time, histological examinations of stiff vessels show abnormal structure of endotheliocytes, increased collagen content, altered elastin molecules, macrophage wall infiltration, increased cytokines content [30]. Moreover, various changes at the molecular level can lead to a 2-4 times thickening of the intima-media and a change in the diameter of the large arteries.

Systemic inflammation, oxidative stress or glycolization of the tissue can cause of the violation of the integrity of molecular compounds. In addition, mineralization of the arterial wall by calcium or phosphorus in association with impaired tonus of the smooth muscle layer, decreased expression of nitric oxide, increased expression of endothelin 1, accumulation of angiotensin 2 and ROS leads to an increase in arterial stiffness [31, 32, 33].

One of the causes of arterial stiffness is visceral obesity. Many pathological conditions are associated with obesity, for example, type 2 diabetes mellitus, arterial hypertension. The hypothetical mechanism that integrates obesity with vascular dysfunction is the contribution of cytokines production by adipose tissue to the development of inflammatory processes, leading to a complex of metabolic disorders, cardiovascular complications, and autoimmune inflammatory diseases. Systemic inflammation and cytokines production are considered as the most important mechanisms by which adipose tissue has a damaging effect on the vascular wall. [34] However, modern treatment methods, including 905 nm LBI, can help reduce the risk of endothelial dysfunction by activating the cascade of immune responses and by enhancing the expression of nitric oxide and restoring the function of NO synthase [35].

Some studies have shown a significant decrease in angiostatin levels in response to the intravenous laser blood clotting, which is a well-known inhibitor of angiogenesis. [36, 37] Taking into account the results, it can be assumed that LILT reduces the level of angiostatin and causes a shift in the balance of pro-angiogenic activity. Therefore, this method can indirectly influence on angiogenesis. Despite the fact that the stimulation of angiogenesis is more likely associated with an increase in the activity of NO synthase, as well as levels of vascular endothelial growth factor (VEGF), several reports confirm this hypothesis [38, 39].

At the same time, long courses of laser therapy not only contribute to the restoration of vascular function, but also significantly increase vascular reactivity. It was confirmed by an improvement in the reaction of blood pressure in response to physical activity. Based on these data, it can be assumed that LBI is a quality alternative for the treatment and prevention of cardiovascular pathologies associated with endothelial dysfunction [40].

Conclusion

The results of various studies confirm that red and infrared light at 600–950 nm has a local and systemic effect on all blood components, cardiovascular and other body systems. Based on the results of various studies over the past years, there is a need to compile a list of diseases that could be treated with the help of ILBI or a safer and easier in use TLBI. Nevertheless, TLBI has a similar to ILBI effect, however, it is a safer and easier to use analogue, since it does not require the presence of physician during the procedure. However, in addition to safety and simplicity, it is worth noting that the use of non-invasive TLBI is more acceptable, because the correct configuration of the device and its incorporation into wearable devices significantly increase the effectiveness of laser therapy.

Due to the positive effect on all aspects of the blood and vascular system, including intracellular molecular processes, laser therapy can improve the work of immune, endocrine and neuroendocrine systems and all metabolic processes. Laser therapy have a positive influence not only on the vascular system, but also on all other body systems, which ultimately will lead to a decrease in the growth of morbidity and vascular complications among the population. Moreover, it could indirectly decrease the number of diseases of other organs and body systems.

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