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Hyperbaric Oxygen Therapy Impact for the Function of Kidney in Metabolic Syndrome (SM) Patients

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A B S T R A C T

Hyperbaric Oxygen Therapy (HBOT) is the therapy of inhaling 100% pure oxygen in a hyperbaric chamber of more than 1 absolute atmosphere. Currently, the use of hyperbaric oxygen therapy is increasingly widespread, not only for decompression sickness and diving problems. But it has been used for clinical therapy, cosmetics, and geriatric care. The American Food and Drug Administration (FDA) has also confirmed various clinical indications, especially those related to metabolic syndromes such as Diabetes Mellitus (DM) and Diabetic Foot Ulcers (DFU). Then how is the use of Hyperbaric Oxygen Therapy for kidney disease? Through this literature review, it is hoped that information will be obtained regarding the effect of Hyperbaric Oxygen Therapy on kidney function, both benefits and side effects, especially in kidney disease due to metabolic syndrome (MetS).

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INTRODUCTION

Kidney disease is a non-communicable disease with a high incidence. Kidney disease has a serious impact up to death, because the kidneys have an important role in the body's metabolism and homeostatic stability. There are many risk factors for kidney disease, one of which is metabolic syndrome. Metabolic syndrome is a collection or combination of various risk factors related to cardiovascular disease. According to data collected by the Indonesia Renal Registry (IRR) in 2014, the number of deaths of hemodialysis patients in Indonesia was 2,221 people with cardiovascular disease as the highest cause of death (59%).

Hyperbaric Oxygen Therapy is one of the oldest treatments in the medical world. This therapy was first initiated around 1662 by Dr. Henshaw from England. However, the development of this therapy did not experience significant progress. Despite hundreds of years, HBOT therapy has had its ups and downs in terms of support and scientific evidence. Along with the development of science and research, now Hyperbaric Oxygen Therapy can be used for clinical therapy according to indications that have been approved by the FDA and UMHS.

Then, what about the effect of Hyperbaric Oxygen Therapy for kidney disease? Are the kidneys included in the indications that are allowed to be given Hyperbaric Oxygen Therapy?

THEORETICAL REVIEW

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METHODOLOGY

Qualitative research is research that is descriptive and tends to use analysis. Process and meaning (subject perspective) are more emphasized in qualitative research. The theoretical basis is used as a guide so that the research focus is in accordance with the facts in the field. Apart from that, this theoretical basis is also useful for providing a general overview of the research setting and as material for discussing research results. There is a fundamental difference between the role of theoretical basis in quantitative research and quantitative research. In quantitative research, research departs from theory to data, and ends

in acceptance or rejection of the theory used; whereas in qualitative research the researcher starts from the data, utilizes existing theory as explanatory material, and ends with a "theory".

RESULT AND DISCUSSION

Metabolic Syndrome and Kidney Disease

Before discussing Hyperbaric Oxygen Therapy, we will first get to know about metabolic syndrome and kidney disease. There are several definitions of metabolic syndrome. In this literature review, the authors used three types of definitions, namely those from the World Health Organization (WHO), NCEP ATP-III and the International Diabetes Federation (IDF). These three definitions can be seen in table 1 below:

Table 1. Criteria for the Definition of Metabolic Syndrome

	WHO (1999)	NCEP (2001)	IDF (2005)
Required	Insulin resistance*		WC† ≥ 94 cm in men or ≥ 80 cm in women
No. of abnormalities	≥ 2 of:	≥ 3 of:	≥ 2 of:
Obesity	WHR > 0.9 in men or > 0.85 in women; BMI ≥ 30 kg/m^2	WC ≥ 102 cm in men or ≥ 88 cm in women	
Triglycerides	≥ 150 mg/dL	≥ 150 mg/dL	≥ 150 mg/dL
HDL cholesterol	< 40 mg/dL in men or < 50 mg/dL in women	< 40 mg/dL in men or < 50 mg/dL in women	< 40 mg/dL in men or < 50 mg/dL in women
Hypertension	≥ 140/90 mmHg	≥ 130/85 mmHg	≥ 130/85 mmHg
Glucose		≥ 110 mg/dL‡	≥ 100 mg/dL
Microalbuminuria	Albumin/creatinine ratio > 30 mg/g; Albumin excretion rate > 20 mcg/min		

Among the components of the metabolic syndrome contained in table 1 above, such as insulin resistance, visceral obesity, high triglyceride levels, and hypertension influence each other in increasing *Reactive Oxygen Species* (ROS). Increased ROS in adipose cells and vascular circulation causes oxidative stress conditions. Oxidative stress is considered as one of the causes of diabetic endothelial-angiopathy dysfunction. Hyperglycemia conditions induce oxidative stress through three pathways, namely; increase in the polyol pathway, increase in glucose auto-oxidation and increase in protein glycosylates.

Oxidative stress also affects the physiology of the vascular system, which causes a decrease in the production of Nitric Oxide (NO) produced by endothelial cells. Decreased NO production causes endothelial dysfunction thereby affecting the diameter of the endothelium. Narrowing of blood vessels can cause hypertension. Hypertension will exacerbate endothelial mechanical damage, so that endothelial inflammation occurs continuously (chronic inflammation). These conditions have an impact on the formation of atherosclerotic plaques and interfere with the work of the cardiovascular system.

Chronic hypertension results in glomerular capillary injury. Increased glomerular capillary pressure for a long time will cause *glomerulosclerosis. Glomerulosclerosis* stimulates hypoxia chronic damage kidney.

The human body has 2 kidneys which are located on the right and left. The kidneys are macroscopically pea-shaped, only about 7-12cm long and 1.5-2.5cm thick. Normal kidney weight is around 120-170 grams.

Kidneys are vital organs that play an important role in maintaining homeostasis (environmental stability in the body), filtering (filtration) and removing waste products from the blood into urine (excretion). In addition to

regulatory and excretory functions, the kidneys also secrete renin. Renin has an important role in regulating blood pressure, plays a role in the formation of vitamin D, regulates calcium and the synthesis of erythropoietin to stimulate red blood cell production.

Kidneys are able to carry out their functions when in a healthy state. If there is interference or disease in the kidneys, this organ will experience a decrease and even lose its ability. As a result, the amount of harmful substances in metabolic waste and electrolyte fluids accumulates in the body. This can have a systemic impact throughout the body.

To find out the decline in kidney function from an early age, kidney function tests can be done with blood and urine tests, including:

1) Blood tests by looking at the levels of creatinine, urea, glomerular filtration rate (GFR)
2) Examination of urine by looking at albumin or protein levels

The best kidney function test is to measure the glomerular filtration rate (GFR). GFR measurement cannot be done directly, but through a formula calculation based on the measurement value of creatinine, gender and age of the patient. So it is called the estimated value of LFG (eLFG).

According to *Chronic Kidney Disease Improving Global Outcomes* (CKD KDIGO) in 2012, the classification of kidney disease is divided into:

Table 2. Classification of Kidney Disease by KDIGO category (2012)

Guide to frequency of monitoring (number of times per year) by GFR and albuminuria category				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min per 1.73 m²) Description and range	G1	Normal or high	⩾90	1 if CKD	1	2
	G2	Mildly decreased	60–89	1 if CKD	1	2
	G3a	Mildly to moderately decreased	45–59	1	2	3
	G3b	Moderately to severely decreased	30–44	2	3	3
	G4	Severely decreased	15–29	3	3	4+
	G5	Kidney failure	<15	4+	4+	4+

GFR and albuminuria grid to reflect the risk of progression by intensity of coloring (green, yellow, orange, red, deep red). The numbers in the boxes are a guide to the frequency of monitoring (number of times per year).

Hyperbaric Oxygen Therapy (Hbot)

Hyperbaric Oxygen Therapy (HBOT) is a therapy that provides oxygen with a concentration of up to 100% and a pressure of more than 1 atmosphere absolute (ATA), which is carried out in a high-pressure air chamber. This therapy can act as the main therapy or complementary therapy.

History of Hyperbaric Therapy started by dr. Henshaw of England who built a hyperbaric chamber in 1662 to treat several types of ailments. Then in 1921, dr. J. Cunningham began to advance the basic theory of using hyperbaric oxygen to treat hypoxic states. However, his efforts failed because he did not have strong scientific evidence.

The 1930s studies on the use of hyperbaric oxygen began to be carried out in a more focused and in-depth manner. Until then around the 1950s, dr. Borrema succeeded in presenting the results of his research on the use of hyperbaric oxygen which dissolves physically in blood fluids, so that it can give life to a state without Hemoglobin which is called *life without blood*. The results of his research on the treatment of gas gangrene with hyperbaric oxygen made him known as the father of RUBT. Since then, hyperbaric oxygen therapy has developed rapidly and continues to this day.

Meanwhile in Indonesia, Hyperbaric Oxygen Therapy was started to be used in 1960 by Lakesla in collaboration with the Naval Hospital dr. Ramelan, Surabaya. At first this Hyperbaric Oxygen Therapy was devoted to the Health of the Navy military and diving. However, over time, this therapy developed and HBOT service centers also spread in various cities in Indonesia.

The working principle of HBOT utilizes the 4 laws of diving physics, namely: (1) Boyle's law: the greater the pressure, the air volume will be smaller and denser, (2) Dalton's law: if the pressure increases, the partial pressure also increases, (3) Henry's law : The higher the partial pressure, the easier it is for the gas to dissolve in the liquid, and (4) Charles' Law: At constant pressure, if the volume of gas increases, the temperature will also increase.

The mechanism of action of HBOT includes several things, namely: (1) Reducing the volume of gas bubbles and accelerating the resolution of gas bubbles, (2) Ischemic and hypoxic areas will receive maximum O2 (hyperoxia), (3) Increase the formation of new capillaries (Angiogenesis/ neovascularization), (4) Suppressing the growth of germs (Antimicrobial), (5) Increasing the formation Fibroblasts, (6) Increase leukocyte phagocytosis, (7) Improve fitness, beauty and geriatric purposes.

As a clinical therapy, HBOT also has appropriate doses that are adjusted to the indications, contraindications and patient needs. The therapeutic dose of HBOT is generally given at 2.4 ATA with 100% pure oxygen according to the dive chart guidelines. Especially in Indonesia, using the Kindwall table composed by Prof. Guritno.

The Role of Hyperbaric Oxygen Therapy on Kidney Function

The benefits of Hyperbaric Oxygen Therapy on kidney function can be seen from the mechanism of action of this therapy. The laws of diving physics Boyle, Dalton, and Henry account for the increased diffusion of oxygen plasma. Under normal air pressure conditions, about 97% of oxygen binds to hemoglobin and about 3% dissolves in blood plasma. Whereas in hyperbaric conditions, oxygen dissolved in blood plasma can increase many times with the amount of hyperbaric pressure applied. Oxygen dissolved in plasma can pass through various atherosclerosis blockages, so that ischemic conditions can be resolved.

In hypoxic conditions, cells that lack oxygen will carry out anaerobic metabolism or fermentation. In anaerobic metabolism, very little ATP is produced, every 1 glucose molecule only produces 2 ATP. So, if a tissue is hypoxic for a long time, there will be mitochondrial damage, energy crisis and cell death.

Hyperbaric Oxygen Therapy can assist in supplying oxygen more quickly at the cellular level (internal respiration), so that metabolism can re-process aerobically. Every one molecule of Glucose that is processed aerobically produces 38 ATP.

Oxygen plays an important role in wound healing. It plays a role in the synthesis and maturation of collagen. Collagen serves as the basic matrix of proliferation. Lack of oxygen will interfere with collagen synthesis. In addition, hyperbaric oxygen therapy also helps stimulate angiogenesis by increasing various *growth factor components*, especially *vascular endothelial growth factor (VEGF)*.

That is why under hypoxic conditions, the wound healing process is relatively longer, and even produces imperfect remodeling products in the form of scar tissue or fibrosis.

Hyperbaric Oxygen Therapy plays a role in increasing *Reactive Oxygen Species (ROS).* ROS will stimulate the formation of antioxidants, such as glutathione, melatonin, and so on, in an effort to balance oxidative stress. Controlled ROS has benefits. On the other hand, if ROS is not controlled, free radicals cause various damage to cells and tissues.

HBOT therapy provides the benefit of reducing swelling or edema through the mechanism of hyperoxia vasoconstriction. Vasoconstriction due to HBOT does not cause hypoxia. This is because the increase in plasma diffusion and microvascular flow keeps oxygen distribution going well.

However, there is one thing that must be understood, the increase and improvement of microvascular blood flow will increase capillary density, so that the ischemia area will experience reperfusion. So that at the beginning of therapy, it is very important to emphasize the principles of safety, comfort, and adaptability.

Hyperbaric oxygen therapy is useful as an antimicrobial. Hyperoxia conditions effectively kill anaerobic bacteria through the process of oxidation of membrane proteins and lipids, damaging DNA, and inhibiting bacterial metabolic functions. In addition, HBOT also increases the action of antibiotics such as fluoroquinolones, amphotericin B, and aminoglycosides which use oxygen for transport across cell membranes.

Based on a study conducted by Rubinstein et al in 2008 on rats, it was found that preconditioning of HBOT in patients with renal ischemia inhibits the decrease in GFR and increases vasodilation, so that treatment with HBOT may be beneficial in ischemic conditions of acute renal failure.

Then in a study conducted by Martin Sedlacek, et al (2021) in thirty-two diabetic patients who had serum levels for 60 days of treatment, the results found no evidence of adverse kidney effects. Patients exposed to the mechanisms of renal injury are more at risk if their kidney function is abnormal at baseline. In addition, the results of a decrease in proteinuria were also found. These data are consistent with data on test animals, as in a study conducted by RJ Ramalho, et al (2012) which showed a decrease in BUN, creatinine, and proteinuria values in experimental rats.

In a study conducted by Purnama, Tjahaya (2015), with a sample of 12 patients with an average age of 55 years suffering from UKD Wagner classification 1-5, the results of assessing their BUN and serum creatinine profiles showed that hyperbaric oxygen therapy did not affect kidney function. Likewise with the study of Kevin T, Terry (2015), the results of statistical tests obtained p = 0.097, so it can be concluded that there was no significant difference between eGFR before and after receiving HBOT therapy in patients with diabetic foot wounds.

In a study conducted by Harison E Laurent, et al (2018), in 35 diabetic patients with UKD who received 30x HBOT therapy sessions (2.4 atm, 90 minutes per session, every day 4-5 days/week). After a month of daily HBOT treatment, significant changes occurred in type 2 diabetes mellitus patients compared with healthy non-diabetic controls, that these changes were responsive to HBOT.

Quoted from the United States Food and Drug Administration (FDA), as of July 26, 2021, permits the use of hyperbaric chambers with support from the Undersea and Hyperbaric Medical Society (UMHS). In these guidelines, HBOT can be used to treat metabolic syndromes such as diabetes, diabetic foot wounds, risk of tissue death, severe and extensive burns, and gas gangrene. However, it is still not approved for treatment of the kidney. This does not mean it cannot, but still requires further research.

CONCLUSION AND RECOMMENDATION

Hyperbaric Oxygen Therapy has benefits in improving the patient's general condition and metabolic syndrome, thereby preventing kidney disease complications. However, HBOT therapy has not made a significant change in kidney function which is characterized by no significant change in the e-GFR value. The effectiveness of HBOT for kidney disease still requires further research with a wider and longer range.

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