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Blood glucose and lipid profile in patients with diabetic foot ulcer that underwent hyperbaric oxygen therapy

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ABSTRACT

Background: Diabetic foot ulcer (DFU) is one of complication in patients with diabetes mellitus. Hyperbaric oxygen therapy (HBOT) is one of adjuvant therapy to increase wound healing on a chronic wound. It may affect biochemical aspect of DFU patient. This study investigates the change in blood glucose levels and lipid profile in the patients with DFU who underwent HBOT.

Methods: Patients with Wagner grade three and four was recruited in this study. The patients divided into two groups (control and HBOT group). A blood sample from all patients was taken before debridement and after 20 sessions of HBOT or 20 days of conventional therapy. We used HBOT 20 sessions at 2.4 ATA (atmosphere absolute) for 90 minutes per session per day.

Results: A total of 32 patients participated in this study. Each group consists of 16 patients. Blood glucose levels were decreased after therapy in each group, but these results were not significant ($p > 0.05$). There was significant increased of LDL cholesterol levels ($p = 0.009$), HDL cholesterol levels ($p = 0.002$), and total cholesterol levels ($p = 0.023$) after therapy in HBOT group, but not in control group. The difference of all blood glucose parameters was not significant ($p > 0.05$). However, the difference in LDL cholesterol, HDL cholesterol, and total cholesterol was significantly different ($p < 0.05$).

Conclusion: There is no significant effect of HBOT to decrease blood sugar, but the significant increase of lipid profile may be caused by the reaction of lipid peroxidation. Increased of lipid profile can be the side effect of HBOT.

Keywords: blood glucose, lipid profile, diabetic foot ulcer, hyperbaric oxygen therapy

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INTRODUCTION

Diabetic foot ulcer (DFU) is one of complication in patients with diabetes mellitus. Patient with diabetes mellitus had approximately 25% for the occurrence of DFU during a lifetime.[1] The DFU requires a long healing time and a multidisciplinary therapy, such as control of blood sugar levels, daily treatment of wounds, proper antibiotic therapy, and surgical revascularization.[2] The ulcer can worsen and lead to amputation of affected lower extremity, estimated 85% cases in Unites States.[1] In addition; patients require a considerable cost to treat DFU, disturbance of daily activities, psychological, social, and quality of life.[1,2] Optimal therapy management can accelerate wound healing and reduce other complications of diabetes mellitus.[1] The standard treatments of DFU were blood glucose regulation, use of antibiotics, ulcer debridement, wound care, offloading (no load or pressure), and improved blood flow or revascularization.[1,2]

Hyperbaric oxygen therapy (HBOT) is one of adjuvant therapy to increase wound healing on a chronic wound.[2,3] Patients breath 100% oxygen at high-pressure chamber 2-3 ATA (atmosphere absolute) for 60-90 minutes per session per day. The number of therapy may vary, from 3 to 5 sessions[3] until 20 or 30 sessions.[2]

This therapy can repair the hypoxic tissue, increase perfusion, reduce edema, decrease inflammatory cytokines, increase fibroblast proliferation, increase collagen production, and promote angiogenesis by the activity of reactive oxygen species (ROS).[2,3] Increase of ROS will improve the regulation of antioxidant enzyme activity of tissue.[2] Effect of HBOT also can decrease blood glucose,[4,5] due to increasing catabolism of glucose.[4]

Obesity animal model showed HBOT could affect of profile lipid, by increasing low-density lipoprotein (LDL) and triglyceride cholesterol and decreasing high-density lipoprotein (HDL) and total cholesterol.[6] This therapy may affect biochemical aspect of DFU patient. This study investigates the change in blood glucose levels and lipid profile in patients with DFU who underwent HBOT.

METHODS

The study was conducted from November 2015 to November 2016 at the Sanglah General Hospital Denpasar Bali. All patients with DFU who came to Sanglah General Hospital were evaluated for their

Wagner classification of DFU. Wagner grade three and four was recruited in this study. The therapy for DFU Wagner grade three and four was surgical debridement. All patients were explained for the procedure of this study, side effects, and benefits. Inclusion criteria were patients aged 18-60 years and diagnosed with diabetes mellitus with DFU Wagner 3 or 4. Exclusion criteria were patients with lung disorders, heart disease, and kidney failure.

A blood sample from all patients was taken before debridement; then we randomized to allocate them into two groups, as control and HBOT group. We test random blood glucose, fasting blood glucose, postprandial blood glucose, LDL cholesterol, HDL cholesterol, triglyceride cholesterol, and total cholesterol.

We used HBOT 20 sessions at 2.4 ATA for 90 minutes per session per day. After 20 sessions of HBOT in HBOT group and conventional therapy for 20 days in the control group, a blood test was repeated. All groups received same conventional therapy for the wound care. We used sterile NaCl 0.9%, sterile gauze, and elastic bandage.

The data were presented as descriptive and bivariate analysis with SPSS 17.0. Shapiro-Wilk test was used to check the normality of data. If the data were normally distributed, pre-test and post-test analysis were done with paired T-test for each group, but if data were not in normal distribution, Wilcoxon test was used. We calculated the difference value between initial and the end of therapy. We used independent T-test to evaluate difference value between control and HBOT group. The value was assumed to be significant at $p < 0.05$.

RESULTS

The total of 32 patients participated in this study. Each group consists of 16 patients. The average age of control group was 60.63 ± 11.34 years, and HBOT group was 51.5 ± 8.23 years. The onset of ulcer was 7.53 ± 12.98 weeks in control group and 5.75 ± 4.19 weeks in HBOT group. The first-time diagnosis of diabetes mellitus in control group was 6.75 ± 6.16 years ago and in HBOT group was 6.33 ± 6.81 years ago.

In control group 68.75% was female, and in HBOT group the percentage for male and female was same. Based on Wagner classification, 56.3% was grade three, and 43.8% was grade four in control group. In HBOT group, the majority of patients with DFU Wagner grade four than grade three (56.3% and 43.8%, respectively).

Table 1 showed comparison value of biochemistry for initial and after therapy in each group. Blood glucose levels assessed by random blood glucose, fasting blood glucose, and postprandial blood glucose. All variables of blood glucose levels were decreased after therapy in each group, but these decreases were not significant ($p > 0.05$). We evaluate lipid profile with LDL cholesterol, HDL cholesterol, triglyceride, and total cholesterol. After therapy in HBOT group, significant increases were observed in LDL cholesterol levels ($p = 0.009$), HDL cholesterol levels ($p = 0.002$), and total cholesterol levels ($p = 0.023$). Triglyceride cholesterol levels in HBOT group after therapy was decreased, but this result was not significant ($p > 0.05$). In control group, HDL cholesterol after therapy was increased

Table 1 Initial and after therapy biochemistry value between groups

	Non-HBOT (n = 16)			HBOT (n = 16)		
Variables	**Pre**	**Post**	**p**	**Pre**	**Post**	**p**
Random blood glucose (mg/dL)	236 (92-493)	193 (111-414)	0.109[b]	238 ± 106.55	191.5 ± 60.91	0.053[a]
Fasting blood glucose (mg/dL)	202.5 ± 75.76	157.69 ± 64.55	0.104[a]	174.5 (105-572)	146 (110-292)	0.365[b]
Post prandial blood glucose (mg/dL)	249.25 ± 87.89	199.19 ± 60.93	0.105[a]	284.19 ± 124.49	247.25 ± 76.29	0.234[a]
LDL cholesterol (mg/dL)	87.06 ± 32.86	76.19 ± 35.66	0.188[a]	52.5 (12-189)	102 (34-291)	0.009[b*]
HDL cholesterol (mg/dL)	22 (11-59)	25.55 (15-58)	0.196[b]	28.66 ± 11.08	40.38 ± 8.72	0.002[a*]
Triglyceride cholesterol (mg/dL)	112 (5-636)	122.5 (10-266)	0.079[b]	141.5 (75-1291)	141 (44-450)	0.278[b]
Total cholesterol (mg/dL)	144.16 ± 55.72	126.14 ± 47.49	0.138[a]	131.2 (54-325)	171.9 (86-417)	0.023[b*]

[a]paired T-test, mean ± standard deviation; [b]Wilcoxon test, median (min-max); [*]p value < 0.05

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Table 2 The difference between initial and after treatment between groups

Value of pre minus post-treatment	Non-HBOT (n = 16)	HBOT (n = 16)	p
Random blood glucose (mg/dL)	68.94 ± 161.8	46.5 ± 88.44	0.63
Fasting blood glucose (mg/dL)	44.81 ± 103.73	29.63 ± 103.13	0.681
Post prandial blood glucose (mg/dL)	50.06 ± 116.07	36.94 ± 119.23	0.755
LDL cholesterol (mg/dL)	10.88 ± 31.54	−39.81 ± 43.92	0.001*
HDL cholesterol (mg/dL)	−1.57 ± 13.08	−11.71 ± 12.24	0.031*
Triglyceride cholesterol (mg/dL)	43.56 ± 132.95	37.44 ± 306.52	0.942
Total cholesterol (mg/dL)	18.02 ± 46.05	−44.04 ± 65.92	0.004*

All values analyzed with independent T-test, mean ± standard deviation; *p-value < 0.05

a little while the other variables were decreased, but these results were not significant ($p > 0.05$).

Table 2 showed the difference value between initial and after therapy for each variable between groups. The decreased of blood glucose parameters (random blood glucose, fasting blood glucose, and postprandial blood glucose) in control groups were higher compared to HBOT group, but these results were not significant ($p > 0.05$). The differences in levels of LDL cholesterol, HDL cholesterol, and total cholesterol was significantly different ($p < 0.05$) between groups, but not significant in triglyceride cholesterol levels.

DISCUSSION

The result from this study found higher decreases of blood glucose in control group when compared with HBOT group, but these results were not significant. The result obtained is in contrast with the study by Karadurmus et al.,[5] in which the fasting blood glucose was significantly different between baseline and after 30 sessions of HBOT ($p < 0.001$). Another study also obtained significant decrease of blood sugar in diabetic patient after 18 sessions of HBOT.[4] In a study involving diabetic rat model; the fasting blood glucose was significantly lower ($p < 0.05$) in hyperbaric group.[6]

Gupta and Sharma[4] found that the decrease in blood glucose occurs because of increased in catabolism, use of glucose, decreased of glucogenic amino acids, and increased of ketogenic amino acids. While Yasuda et al[6] showed, HBOT could improve glucose tolerance and insulin resistance. This mechanism can significantly lower insulin level and improve insulin sensitivity.[6] Another variable to evaluate blood glucose was glycated hemoglobin (HbA1c), and in some study, this marker was significantly decreased.[4,5] This marker can be considered for future research.

The hyperglycemic condition, which occurs in diabetes mellitus, can cause oxidative stress and result in increased production of ROS. On the other hand, HBOT can also increase ROS.[2,7] In low concentration, ROS acts as cellular messengers to regulate wound healing such as growth factors, cells proliferation and migration, angiogenesis, and extracellular matrix synthesis.[2] The production of ROS also occur through lipid peroxidation and protein,[7-9] which will improve the regulation of antioxidant enzyme activity of tissue.[2,7-9]

In this study, the patients may sustain from oxidative stress, either derived from HBOT or the disease itself. Oxidative stress in diabetes mellitus takes place due to hyperglycemia which occurs in such patients.[10] Various studies found that patients with diabetes tend to have more oxidative cells and increase in ROS generation than healthy individuals.[11-13] Several related pathways are thought to be responsible for the generation of ROS in diabetic patients, i.e. polyol pathway, hexosamine pathway, protein kinase C (PKC) pathway, and advanced glycation end products (AGEs) formation. The PKC pathway induces the activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and nuclear factor-kappaB (NF-κB), responsible for excessive ROS production. Furthermore, binding to AGE receptors may induce the production of ROS. Polyol pathway does not directly generate ROS. However, it involved in redox imbalance and causing oxidative stress.[14]

In our study, the decrease in blood glucose in the HBOT group was lower than the control group. It may be due to the increase of oxidative stress from the high concentration of oxygen exposure. Oxidative stress may lead to insulin resistance and a decrease in insulin secretion, thus resulting in higher blood glucose. No complete mechanism is known which responsible for insulin resistance. However several mechanisms of ROS in insulin resistance has been proposed. An increase in the hexosamine pathway, decrease in GLUT4 gene transcription and increase in GLUT1 linked to insulin resistance.[15,16] As for the decrease in insulin secretion, chronic oxidative stress derived from glucose oxidation pathway may lead to increase of mitochondrial superoxide production and activates uncoupling protein-2 (UCP-2). The protein decreases the ATP/ADP relationship through proton leak in the beta cells, which reduce insulin secretion.[17,18] The cumulative result of insulin resistance and a decrease in insulin secretion derived from ROS may be responsible for the lower decrease of blood glucose in HBOT group, in which this therapy may generate more ROS.

Our study had significantly improved HDL-cholesterol (p = 0.031). This result was in accordance with a study by Karadurmus et al.,[5] in which the HDL cholesterol levels was significantly increased ($p < 0.001$). However, their study showed a significant decrease of LDL cholesterol levels after HBOT with $p < 0.001$.[5]

This result is in contrast with our study, in which the LDL cholesterol was significantly increased in HBOT group (p = 0.009), and the difference between control and treatment group was significantly different (p = 0.001).

A study by Tsuneyama et al[19] in animal model obtained increased in triglyceride, increased in LDL cholesterol, decreased in HDL, and decreased in total cholesterol in HBOT group when compared with non-HBOT group, but these results were not significant. The results were in contrast with our study; we found significant increased of LDL cholesterol levels (p = 0.009), significant increased of HDL cholesterol levels (p = 0.002), and significant increased of total cholesterol levels (p = 0.023), but not significant decreased of triglyceride cholesterol.

The lipid may be migrated into the blood and stored in hepatocellular, which can cause organ damage.[19] Patient with metabolic syndrome had a complex reaction with HBOT, since the increase in oxygen may improve tissue oxygen, increasing proliferation, higher wound healing, and kill anaerobic bacteria. However, the side effect of an increase in oxygen was higher oxidative stress in tissue. Further investigation must be conducted to reduce the adverse effect of oxidative stress.

Lipid peroxidation had a relationship with high blood glucose and high oxidative stress in diabetic patients. In a clinical study, there was a significant association of higher lipid peroxidation with high fasting blood glucose and high HbA1c levels.[9] Evaluation of end product of lipid peroxidation were malondialdehyde (MDA), propanal, hexanal, and 4-hydroxynonenal (4-HNE).[8] Another study can evaluate antioxidant levels in the body which can change during HBOT.

CONCLUSION

There is no significant effect of HBOT to decrease of blood sugar, but significant increase of lipid profile may be caused by the reaction of lipid peroxidation. Increased of lipid profile can be the side effect of HBOT and further research to investigate disadvantages of increased in lipid profile is needed.

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